07, 036124

DA C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

In re patent: ATSUMI et al.
Patent No.: 4,839,350
Issued: June 13, 1989
For: CEPHALOSPORIN COMPOUNDS AND THE PRODUCTION THEREOF

Examiner:
Art Unit:
Docket No.: G000000644/BAS

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231
SIR:

Attached is:

____ a response after Final Rejection dated
____ a response to the Office Action dated
____ a Preliminary Amendment
____ a Petition for an extension of time
X Other: Application for Extension of Patent Term w/Attachments 1-4; Certified Duplicate Copy of Application for Extension of Patent Term w/Attachments 1-4; and Appointment of Power of Attorney.

Fees: For claims if required and/or other fees as shown below:

	NOW	Previously Paid For	Present Extra	Rate	$
__ TOTAL CLAIMS				X $ 18 =	
__ INDEP. CLAIMS				X $ 84 =	
TOTAL OF ABOVE CLAIMS FEES =					
__ Reduction by ½ for **small entity status** of applicant					
SUBTOTAL =					
__ Fee for extension of time (per attached Petition)					
X Other fee for Application for Term Extension					1120.00
TOTAL OF ALL FEES =					1120.00

X A check in the amount of $1120.00 is enclosed. If no check or an insufficient check is enclosed and a fee is due in connection herewith, the Commissioner is authorized to charge any fee or additional fee due in connection herewith to Deposit Account No. 12-0555. A duplicate of this sheet is enclosed.

X In the event that a petition for extension of time is required to be submitted herewith and that a separate petition is not submitted herewith, applicant hereby petitions under 37 CFR 1.136(a) for an extension of time of as many months as are required to render this submission timely. Any fee is authorized above.

Respectfully submitted,

Date: October 17, 2001

By: B. Aaron Schulman
Registration No.: 31,877

LARSON & TAYLOR, PLC • 1199 North Fairfax St. • Suite 900 • Alexandria, VA 22314

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE *PATENT*

In re patent: ATSUMI et al.
Patent No.: 4,839,350
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	NOW	*Previously Paid For*	*Present Extra*	*Rate*	$
___ TOTAL CLAIMS				X $ 18 =	
___ INDEP. CLAIMS				X $ 84 =	
				TOTAL OF ABOVE CLAIMS FEES =	
___ Reduction by ½ for **small entity status** of applicant					
				SUBTOTAL =	
___ Fee for extension of time (per attached Petition)					
X Other fee for Application for Term Extension					1120.00
				TOTAL OF ALL FEES =	1120.00

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Respectfully submitted,

Date: October 17, 2001

By: B. Aaron Schulman
Registration No.: 31,877

LARSON & TAYLOR, PLC • 1199 North Fairfax St. • Suite 900 • Alexandria, VA 22314

IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

PATENT

In re patent of: Atsumi, et al.
Patent No.: 4,839,350
Issued: June 13, 1989
For: CEPHALOSPORIN COMPOUNDS AND THE PRODUCTS THEREOF

Atty Docket No.:
G000000644/BAS

APPOINTMENT OF POWER OF ATTORNEY

Assistant Commissioner of Patents
Washington, D.C. 20231

SIR:

I, Mr. Ichiro Kitasato, the president and representative of Meiji Seika Kaisha, Ltd., the owner of record of the above-identified patent:

appoint the practitioners of LARSON & TAYLOR, PLC associated with the Customer Number provided below to apply for a patent term extension for this patent and to transact all business in the Patent and Trademark Office connected therewith on behalf of Meiji Seika Kaisha, Ltd., and direct all correspondence be sent to that Customer Number.

CUSTOMER NUMBER: 00881

Date: This 16th day of July, 2001

Ichiro Kitasato

Ichiro Kitasato
President, Meiji Seika Kaisha, Ltd.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RE: U.S. Patent No. 4,839,350

ISSUED: June 13, 1989

TO: ATSUMI et al.

FOR: CEPHALOSPORIN COMPOUNDS AND THE PRODUCTION THEREOF

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 AND 37 C.F.R. §1.710

Commissioner of Patents and Trademarks
Washington, D.C. 20231

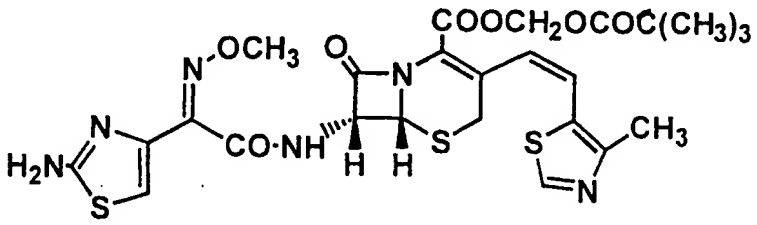
Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. Sec 156, Meiji Seika Kaisha Ltd., 4-16, Kyobashi 2-Chome, Chuo-ku, TOKYO, JAPAN, owner of the above identified patent, hereby requests an extension of the patent term of U.S. Patent No. 4,839,350, covering SPECTRACEF (Cefditoren pivoxil). TAP Pharmaceutical Products Inc., which applied for the commercial marketing approval, is licensee from Meiji Seika Kaisha, Ltd. which is the assignee under the patent in the United States of America.

Applicant submits this application for the extension of the patent term of U.S. Patent No. 4,839,350 by providing the following information organized corresponding to 37 C.F.R. §1.740.

(1) The approved product is identified as SPECTRACEF (Cefditoren pivoxil). SPECTRACEF is indicated in the therapeutic treatment of various bacterial infectious diseases. It contains a compound having the chemical name (-)-(6R,7R)-2,2-

dimethylpropionyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate and structure:



The compound is a pro-drug such that when its ester moiety is hydrolyzed by an enzyme in the body subsequent to its prompt absorption through the digestive tubes, the cephem compound formed in the form of a free carboxylic acid exhibits strong antibacterial activities.

(2) The regulatory review period occurred under section 505(b) of the Federal Food, Drug and Cosmetic Act (FFDCA). Section 505(b) provides for the submission and approval of new drug applications (NDAs) for drug products, which would include drugs for the therapeutic treatment of various bacterial infectious diseases.

(3) SPECTRACEF was approved by the Food and Drug Administration (FDA) for commercial marketing under section 505(b) of the FFDCA on August 29, 2001.

(4) SPECTRACEF contains as the active ingredient (-)-(6R,7R)-2,2-dimethylpropionyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. This active ingredient has not previously been approved for commercial marketing or use under 505(b) of the FFDCA.

(5) The product was approved for commercial marketing on August 29, 2001. This application is being submitted within the permitted period, the last day within the sixty day period permitted for submission of an application for extension being October 28, 2001.

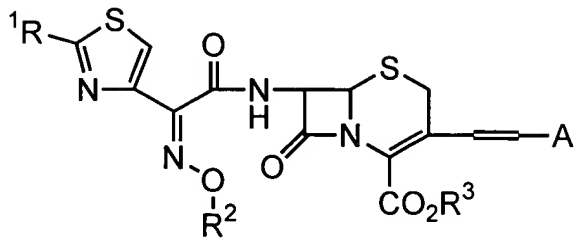
(6) The patent for which patent term extension is sought is U.S. Patent No. 4,839,350, which issued on June 13, 1989, naming Kunio Atsumi, Kenji Sakagami, Yuichi Yamamoto, Takashi Yoshida, Ken Nishihata, Shinichi Kondo and Shunzo Fukatsu as the inventors for CEPHALOSPORIN COMPOUNDS AND THE PRODUCTION THEREOF. The term of the patent has never been extended and has not yet expired. The patent will expire on June 13, 2006.

(7) A complete copy of U.S. Patent No. 4,839,350 in the prescribed form is attached as Attachment 1.

(8) A copy of the maintenance fee statements for U.S. Patent 4,839,350 indicating that the maintenance fees have been paid is attached as Attachment 2.

(9) Applicant states that U.S. Patent No. 4,839,350 claims the approved product and its hydrolyzed product and pharmaceutical antibacterial composition which comprises an antibacterially effective amount of the approved product in the following applicable claims:

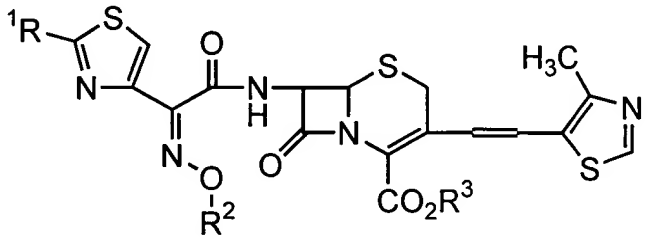
1. A cephalosporin compound of the formula (I)



(I)

wherein R^1 is an amino group or a protected amino group; R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group; R^3 is a hydrogen atom, a salt-forming cation or a carboxylprotecting group; A is thiazolyl group, a lower-alkylthiazolyl group, a halo-thiazolyl group, or a 3-lower-alkylthiazolio group optionally substituted with one lower alkyl group, with an iodide or trifluoroacetate counterion, and a pharmaceutically acceptable salt or ester of said cephalosporin compound.

2. A cephalosporin compound as claimed in claim 1 which is of the formula (Ic)



(Ic)

wherein R^1 is an amino group or a protected amino group; R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, and R^3 is a hydrogen atom, a salt-forming cation or a carboxylprotecting group.

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6. A compound as claimed in claims 1, 2, 3, 4 or 5 in which R^1 is an amino group; R^2 is a methyl group or a carboxymethyl group, and R^3 is sodium atom, benzhydryl group, p-methoxybenzyl group, diphenylmethyl group, pivaloyloxymethyl group or (5-methyl-2-oxo-1,3-dioxolene-4-yl)-methyl group.

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12. 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]–3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) pivaloyloxymethyl ester.

13. A compound which is selected from the group consisting of 7-[2-methoxyimino-2-(2-aminothiazol-4-yl]acetamido-3-[2-(4-methylthiazol-5-yl)vinyl] –3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer), a sodium salt thereof, a pivaloyloxymethyl ester thereof, a (5-methyl-2-oxo-1,3-dioxolene-4-yl)-methyl ester thereof and an acid addition salt thereof with trifluoroacetic acid.

14. A pharmaceutical, antibacterial composition which comprises an antibacterially effective amount of the compound of the formula (I) as defined in claim 1 or the compound of the formula (Ic) to (If) as defined in anyone of claims 2 to 5 or a pharmaceutically acceptable salt or ester thereof, as the active ingredient, in combination with a pharmaceutically acceptable carrier for the active ingredient.

The above claims read on the approved product in that FDA has approved SPECTRACEF whose active ingredient is the cephalosporin compound recited in Claim 12. Claims 1, 2, and 6 are broader claims which encompass cephalosporin compound recited in Claim 12. In Claim 13, the approved product and its hydrolyzed product are claimed. Claim 14 is the composition claim, which comprises an antibacterially effective amount of the approved product.

(10) Applicant states that the relevant dates and information pursuant to 35 U.S.C. §156(g) are as follows:

(a) Effective date of IND No. 53,866 – August 30, 1997

(b) NDA No. 21-222 initially submitted to FDA on December 29, 1999

(c) NDA No. 21-222 approved by FDA on August 29, 2001

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached as Attachment 3. In addition, a copy of the FDA approved labeling for the product is attached as Attachment 4.

(12) In the opinion of the applicant, this patent is eligible for the requested extension of 1032 days (2.83 years) because, the term of the patent has not yet expired, the term of the patent has never been extended, the application for extension is submitted by the owner of record of the patent, the product has been subject to a regulatory review period before its commercial marketing or use, and permission for the commercial marketing of the product is the first permitted commercial marketing of the product under the provision of law under which the regulatory review occurred.

Applicant respectfully states that it is entitled to an extension of 1032 days which was calculated as follows:

> The period from the effective date of IND (August 30, 1997) to the effective date of receipt by the FDA of the NDA (21-222) on December 29, 1999, is 2 years, 3 months, and 29 days (or 851 total days); half this period is 425 days. Applicant submits that applicant acted with due diligence and therefore the relevant IND period of 425 days should not be reduced.
>
> The regulatory review period started on August 30, 1997, the day that the IND 53,866 became effective under section 505(i) of the FFDCA.
>
> The period from the date of receipt by the FDA of NDA (21-222) on December 29, 1999 to the date of NDA approval on August 29, 2001 is 1 year, 7 months, 30 days (or 607 total days). Applicant also submits that applicant acted with due diligence during the NDA regulatory review period and that the relevant NDA period of 607 days should not be reduced.
>
> The total sum of the possible extension is 1032 days as calculated by the following method: 425 days + 607 days = 1032 days or 2.83 years

Thus, Applicant is requesting a patent extension of 2 years and 301 days (1032 days), so the extended patent will expire on 04/10/2009.

Since a request was not submitted for an exemption under 505(i) of the FFDCA before September 24, 1984 and the commercial marketing of the product was not approved before September 24, 1984, section 37 C.F.R. § 1.775(d)(6)(ii)(A) does not apply.

(13) Applicant acknowledges the duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought in this application for extension of the patent term.

(14) A check covering the patent term extension fee under 37 C.F.R. § 1.20(j)(1) of $1120.00 is enclosed with this application.

(15) Inquiries and correspondence relating to this application for patent term extension are to be directed to:

B. Aaron Schulman
LARSON & TAYLOR, PLC
1199 North Fairfax Street
Suite 900
Alexandria, Virginia 22314-1437
(703) 739-4900

(16) This application for extension of the patent term is being submitted in duplicate, as certified below.

(17) The undersigned hereby declares that he is a patent attorney authorized to practice before the United States Patent and Trademark Office and has general authority from Applicant, Meiji Seika Kaisha Ltd., for the purpose of transacting all matters reasonably related to obtaining an extension of patent term for U.S. Patent No. 4,839,350, to act on its behalf in patent matters (Appointment of Power of Attorney is included with this application); that he has reviewed and understands the contents of the application being submitted pursuant to 35 USC 156; that he believes the patent is subject to extension pursuant to 37 C.F.R. § 1.710; that he believes an extension of the length claimed is fully justified under 35 USC 156 and the applicable regulations; and that he believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

Respectfully submitted,
LARSON & TAYLOR, PLC

Date: October 17, 2001

B. Aaron Schulman
Reg. No. 31, 877
Attorney for Applicant
Meiji Seika Kaisha Ltd.

Atty. Docket No.: G000000644/BAS
1199 North Fairfax Street
Suite 900
Alexandria, Virginia 22314-1437
(703)739-4900

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.

Donald J. Quigg

Commissioner of Patents and Trademarks

Priscilla A. Fuller

Attest

United States Patent [19]

Atsumi et al.

[11] **Patent Number: 4,839,350**

[45] **Date of Patent: Jun. 13, 1989**

[54] **CEPHALOSPORIN COMPOUNDS AND THE PRODUCTION THEREOF**

[75] Inventors: **Kunio Atsumi; Kenji Sakagami,** both of Kawasaki; **Yuichi Yamamoto,** Yokohama; **Takashi Yoshida,** Tokyo; **Ken Nishihata; Shinichi Kondo,** both of Yokohama; **Shunzo Fukatsu,** Tokyo, all of Japan

[73] Assignees: **Meiji Seika Kaisha, Ltd.; Susumu Mitsuhashi,** both of Tokyo, Japan

[21] Appl. No.: **36,124**

[22] Filed: **Apr. 7, 1987**

Related U.S. Application Data

[63] Continuation of Ser. No. 769,746, Aug. 27, 1985, abandoned.

[30] **Foreign Application Priority Data**

Sep. 7, 1984 [JP] Japan 59-186464
Jul. 18, 1985 [JP] Japan 60-157005

[51] **Int. Cl.**[4] **A61K 31/545;** C07D 501/24

[52] **U.S. Cl.** **514/202;** 514/206; 540/222; 540/227

[58] **Field of Search** 540/222, 227; 514/202, 514/206

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,255,423	3/1981	Beattie	540/222
4,307,116	12/1981	Farge	540/227
4,482,551	11/1984	Furlenmeier	540/227

FOREIGN PATENT DOCUMENTS

0053074 6/1982 European Pat. Off. .

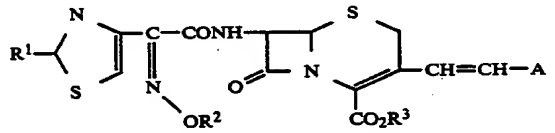
OTHER PUBLICATIONS

Dunn, J. Antimicrobial Chemotherapy (1982), 10, Supplement C, pp. 1–10.

Primary Examiner—Robert J. Warden
Assistant Examiner—Robert Benson
Attorney, Agent, or Firm—Larson and Taylor

[57] **ABSTRACT**

A class of new caphalosporin compounds (syn-isomer) is now provided, which is useful as antibacterial agent and is represented by the general formula (I)



wherein R^1 is an amino group or a protected amino group; R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group; R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group; A is an unsubstituted or substituted phenyl group, an unsubstituted or substituted furyl group, an unsubstituted or substituted thiazolyl group or an unsubstituted or substituted 3-lower-alkylthiazolio group, and a pharmaceutically acceptable salt or ester thereof.

14 Claims, No Drawings

CEPHALOSPORIN COMPOUNDS AND THE PRODUCTION THEREOF

This application is a continuation of application Ser. No. 769,746, filed Aug. 27, 1985, now abandoned.

SUMMARY OF THE INVENTION

This invention relates to a new cephalosporin compound and a pharmaceutically acceptable salt or ester thereof which are useful as antibacterial agent. More particularly, this invention relates to a new cephalosporin compound (as syn-isomer) which bears an α-(substituted imino)-α-(2-aminothiazolyl)-acetyl group as a side chain at the 7-position and a β-substituted vinyl group as a side chain at the 3-position of the cephem nucleus. This invention also relates to a pharmaceutical composition comprising the new cepahlosporin compound as active ingredient. This invention further relates to a process for the production of the new cephalosporin compound.

BACKGROUND OF THE INVENTION

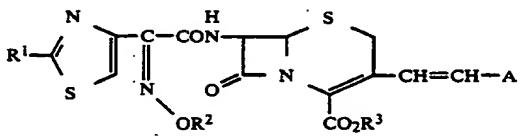
Some β-lactam compounds which are closely related to the new cephalosporin compounds of this invention are known as disclosed in Japanese Patent Application first publication "Kokai" No. 124790/80, No. 122383/81 and No. 76088/84, and U.K. patent application first publication No. 2128990 A. These known cephalosporin compounds which are disclosed in said Japanese patent application first publications have a β-substituted vinyl group as the side chain at the 3-position of the cephem nucleus, similarly to the cephalosporin compounds according to this invention. However, the new cephalosporin compounds of this invention are different from the above-mentioned known cephalosporin compounds in respect of the kind of the substituent born on the β-position of the β-substituted vinyl group at the 3-position of the cephem nucleus.

Cephalosprin-type antibiotics are known to be highly and broadly active against a variety of gram-positive and gram-negative bacteria. Various kinds of semi-synthesized cephalosporin compounds have already been available commercially and applied clinically for the therapeutic treatment of various infections diseases. But, only a very few ones amongst these semi-synthesized cephalosporin compounds are practically effective against the strains of bacteria of the genus Pseudomonas and Proteus. These known cephalosporin compounds are also degradable by a β-lactamase which is produced by some resistant strains of bacteria, and they exhibit only a poor activity against some resistant strains of bacteria which have now been a target of clinical treatments of bacterial infections (see: W. E. Wick "Cephalosporins and Penicillins, Chemistry and Biology", edited by E. H. Flynn, Academic Press, New York, N.Y., 1972, Chapter 11.)

We, the present inventors, have now succeeded in preparing new cephalosporin compounds represented by the general formula (I) shown below, and have found that said new cephalosporin compounds exhibit activity in a very wide range of the antibacterial spectrum and that these new compounds are highly active not only against a variety of gram-positive and gram-negative bacteria but also against some resistant strains of bacteria.

DETAILED DESCRIPTION OF THE INVENTION

According to a first aspect of this invention, there is provided a new cephalosporin compound of the general formula (I)



(I)

wherein R^1 is an amino group or a protected amino group; R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group; R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group; A is an unsubstituted or substituted phenyl group, an unsubstituted or substituted furyl group, an unsubstituted or substituted thiazolyl group or an unsubstituted or substituted 3-lower-alkylthiazolio group, and a pharmaceutically acceptable salt or ester of said cephalosporin compound.

The cephalosporin compound of the formula (I) according to this invention includes two isomers, namely (E)-isomer (i.e., a trans-isomer) and (Z)-isomer (i.e., a cis-isomer), depending on the relative positions of the substituents and the hydrogen atoms attached to the vinylic double bond of the β-substituted vinyl group at the 3-position of the cephem nucleus. The cephalosporin compound of this invention, therefore, covers the (E)-isomer, the (Z)-isomer and the mixture thereof. The (Z)-isomer of the cephalosporin compound according to this invention is of such a form in which the group A and the cephem moiety take "cis"-position around the vinylic double bond of the vinyl group at the 3-position as shown in the general formula (I). The (E)-isomer of the cephalosporin compound is of such form in which the group A and the cephem moiety take "trans"-position aroung the vinylic double bond of the vinyl group at the 3-position of the cephem nucleus.

Some of the terms used in this specification have the meanings as defined below:

The term "lower" means that an alkyl or alkoxyl or alkanoyl group concerned is containing 1 to 6 carbon atoms, unless otherwise stated. The amino-protecting group, such as the amino-protecting group present in the protected amino group which R^1 may represent, includes a conventional amino-protecting group which may easily be removed by acid hydrolysis, for example, an alkoxycarbonyl group such as tert.-butoxycarbonyl group; and acyl group such as a formyl group and a chloroacetyl group; and a trityl group.

The "protected carboxymethyl group" which R^2 represents is such a carboxymethyl group of which the carboxyl group has been protected by esterification with a lower alkyl group, e.g., methyl, ethyl, propyl, n-butyl and t-butyl or an aryl group such as phenyl or an aralkyl group such as benzyl.

The salt-forming cation which R^3 represents is a conventional metal cation and may include cation of an alkali metal, an alkaline earth metal and ammonium. Sodium cation is preferred. The carboxyl-protecting group which R^3 represents is a carboxyl-protecting group conventionally used for cephalosporins and may include an aryl group, a lower alkyl group, a lower-alkoxymethyl group, a lower-alkylthio methyl group

and a lower-alkanoyloxymethyl group and the like. The group R^3 may also include a metabolically unstable group which is easily hydrolyzed and cleaved in vivo and which may include, for example, a lower-alkoxycarbonyloxyalkyl group, a lower-alkylcarbonyloxyalkyl group, an unsubstituted or substituted (2-oxo-1,3-dioxolene-4-yl) methyl group and the like.

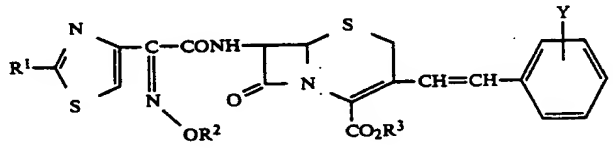
"Unsubstituted or substituted phenyl group" which A represents includes a phenyl group; a phenyl group having a lower alkyl substituent, for example, p-tolyl; a halogenated phenyl group such as o-fluorophenyl, and a lower alkoxyphenyl group such as p-anisyl.

"Unsubstituted or substituted furyl group" which A represents includes a 2-furyl group, a 3-furyl group and a 5-nitro-2-furyl group.

"Unsubstituted or substituted thiazolyl group" which A represents includes thiazol-2-yl group, thiazol-4-yl group, thiazol-5-yl group, a 2-lower-alkylthiazol-5-yl group (e.g., 2-methylthiazol-5-yl), 4-methylthiazol-5-yl group, a 4-halo-thiazol-5-yl group and a 2,4-di-halo-thiazol-5-yl group.

"Unsubstituted or substituted 3-lower-alkylthiazolio group" which A represents includes a 3,4-dimethyl-5-thiazolio group.

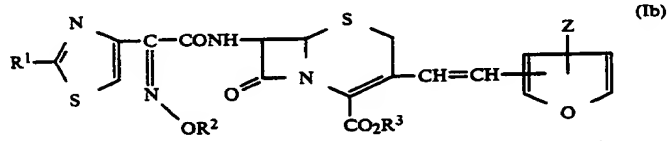
According to a preferred, first embodiment of the first aspect invention, there is provided a cephalosporin compound of the general formula (Ia)



(Ia)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, and Y is a hydrogen atom, a lower alkyl group, a lower alkoxyl group or a halogen atom.

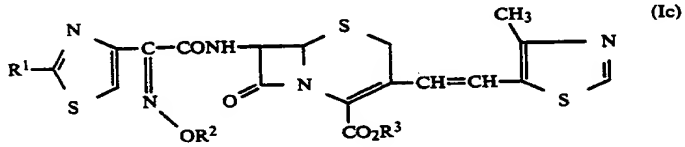
According to a preferred, second embodiment of the first aspect invention, there is provided a cephalosporin compound of the general formula (Ib)



(Ib)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, Z is a hydrogen atom, nitro group or a halogen atom.

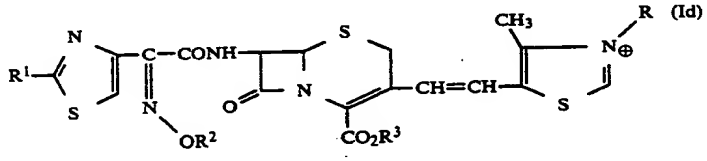
According to a preferred, third embodiment of the first aspect invention, there is provided a cephalosporin compound of the general formula (Ic)



(Ic)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, and R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group.

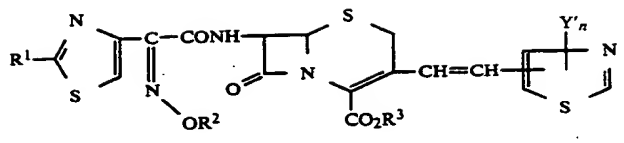
According to a preferred, fourth embodiment of the first aspect invention, there is provided a cephalosporin compound of the general formula (Id)



(Id)

wherein R^1 is an amino group or a protected amino group, R^2 is a lwoer (C_1–C_6) alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, and R is a lower alkyl group.

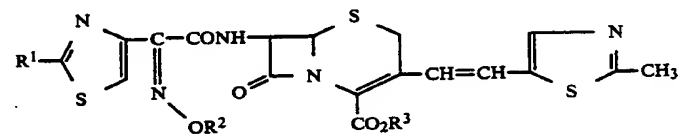
According to a preferred, fifth embodiment of the first aspect invention, there is provided a cephalosporin compound of the general formula (Ie)



(Ie)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower (C_1–C_6) alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, and Y' is a hydrogen atom or a halogen atom, and n is a whole number of 1 or 2.

According to a preferred, sixth embodiment of the first aspect invention, there is provided a cephalosporin compound of the generäl formula (If)



(If)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower (C_1–C_6) alkyl group, a carboxymethyl group or a protected carboxymethyl group, and R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group.

Preferred examples of the new cephalosporin compound of the formula (I) or of the formula (Ia) to (If) according to this invention are listed below:

(A) 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-(2-phenylvinyl)-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(B) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-(2-phenylvinyl)-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(C) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(o-fluorophenyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(D) 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(2-o-fluorophenyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(E) 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(F) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(G) 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(5-nitro-2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(H) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(5-nitro-2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(I) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-2-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(J) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-4-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(K) 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(thiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(L) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or cyn-isomer, cis-isomer).

(M) 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or cyn-isomer, cis-isomer).

(N) 7-[2-t-butoxycarbonylmethoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(O) 7-[2-carboxymethoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(P) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (cyn-isomer, trans-isomer, or cyn-isomer, cis-isomer).

(Q) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(R) 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(S) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or cyn-isomer, cis-isomer).

(T) 7-[2-methoxyimino-2-(2-amino-thiazol-4-yl)acetamido]-3-[2-(2,4-dichlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer).

(U) 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(3,4-dimethyl-5-thiazolio)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) iodide or trifluoroacetate.

(V) 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(3,4-dimethyl-5-thiazolio)vinyl]-3-

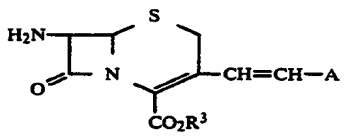
cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) iodide or trifluoroacetate.

Each of the particular cephalosporin compounds as listed above may also be in the form of its carboxylate (at the carboxyl group at the 2-position of the cephem nucleus), for example, its sodium salt, its methyl ester, its ethyl ester, its diphenylmethyl ester, its p-methoxybenzyl ester, its pivaloyloxymethyl ester and its (5-methyl-2-oxo-1,3-dioxolene-4-yl)methyl ester.

The new compound of the formula (I) according to this invention may be prepared by any one of the following two methods.

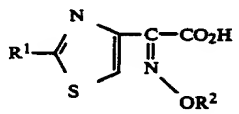
Method 1:

In this method 1, a 7-aminocephalosporanic acid compound of the formula (II)



(II)

wherein R^3 and A are as defined above, or a reactive derivative (such a derivative made reactive at the 7-amino group as shown in the formula) of the compound of the formula (II) or a salt thereof is reacted with a 2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetic acid compound of the formula (III)



(III)

wherein R^1 and R^2 are as defined above, or a reactive acid derivative (such a derivative made reactive at the carboxyl group as shown in the formula) of the compound of the formula (III) or a salt thereof.

Examples of the reactive derivative at the amino group of the compound (II) include such an imino derivative of Shiff-base type which may be obtained by reaction of the compound (II) with a carbonyl compound such as an aldehyde or ketone, or an enamine-type isomer (tautomer) of said imino derivative; such a silyl derivative which may be obtained by reaction of the compound (II) with a silyl compound such as bis-(trimethylsilyl)acetamide; or such a derivative which may be obtained by reaction of the compound (II) with phosphorus trichloride or phosgene.

Appropriate examples of the salts of the compound (II) or (III) include an acid-addition salt thereof, for example, a salt of the compound (II) or (III) with an organic acid such as acetic acid, maleic acid, tartaric acid, benzenesulfonic acid, toluenesulfonic acid; a salt of the compound (II) or (III) with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid; a metal salt (carboxylate) of the compound (II) or (III) with an alkali metal such as sodium and potassium or with an alkaline earth metal such as calcium and magnesium; ammonium salt (carboxylate) of the compound (II) or (III); an amine salt of the compound (II) or (III) with an organic amine such as triethylamine and dicyclohexylamine.

Suitable examples of the reactive derivative at the carboxyl group of the compound (III) include an acid halide, an acid azide, an acid anhydride, an activated amide and an activated ester of the compound (III), and especially they may be an acid chloride or an acid bromide of the compound (III); a mixed acid anhydride of the compound (III) with an acid, for example, with a substituted phosphoric acid such as dialkylphosphoric acid, phenylphosporic acid, diphenylphosphoric acid, dibenzyl-phosphoric acid, a halogenated phosphoric acid, with a dialkyl phosphosphoric acid, with sulfurous acid, with thio-sulfuric acid, with sulfuric acid, with an alkyl carbonate such as methyl carbonate and ethyl carbonate, with an aliphatic carboxylic acid such as pivalic acid, valeric acid, isovaleric acid, 2-ethylacetic acid and trichloroacetic acid, or with an aromatic carboxylic acid such as benzoic acid; a symmetrical acid anhydride of the compound (III); an activated amide of the compound (III) formed with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester of the compound (III) such as cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenylthio ester, p-cresylthio ester, carboxymethylthio ester, pyranyl ester, pyridyl ester, piperidyl ester or 8-quinolylthio ester; or an ester of the compound (III) formed with a N-hydroxyl compound such as N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxy-6-chloro-1H-benzotriazole.

These reactive derivatives of the compound (II) may be properly selected depending on the nature of the compound (III) to be reacted therewith.

The reaction of condensing the compound (II) with the compound (III) may usually be conducted in a conventional unreactive solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofurane, ethyl acetate, N,N-dimethylformamide, pyridine, or in any other solvent which exerts no adverse effect on the progress of this reaction. These solvents may be used as a mixture with water.

In the case where the compound (III) is used in the form of a free acid or in the form of a salt, the reaction may preferably be conducted in the presence of a condensing agent. Examples of such a condensing agent may be N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; phosphorous acid trialkylester; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride; phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzoisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide (intramolecular salt); 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; Vilsmeier reagent as prepared from reaction of dimethylformamide with thionyl chloride, phosgene and phosphorus oxychloride.

This reaction according to Method 1 may also be conducted in the presence of an inorganic or organic base. Examples of these inorganic and organic bases may be an alkali metal hydrogen carbonate such as sodium hydrogen carbonate or potassium hydrogen

carbonate, an alkali metal carbonate such as sodium carbonate or potassium carbonate, an alkaline earth metal carbonate such as calcium carbonate, a tri-(lower-)alkyl amine such as trimethylamine or triethylamine, pyridine, N-(lower)alkylmorpholine, N,N-di-(lower)alkylbenzylamine.

The reaction as above may be carried out at a noncritical temperature, and may usually be conducted under cooling or under heating.

The product compound of the formula (I) which has been prepared by the above reactions for the preparation thereof, if desired, may then be subjected to further conventional step(s) for removal of the remaining carboxyl-protecting group and/or the remaining amino-protecting group therefrom, and/or to further conventional step(s) for converting the carboxyl group(s) of the product compound (I) into a metabolically unstable, non-toxic ester (carboxylate) group. The method for removal of the carboxyl-protecting group and/or the amino-protecting group may properly be chosen according to the nature of the protecting groups to be removed.

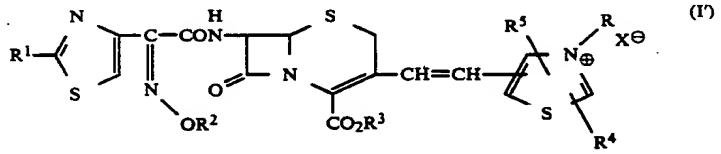
The amino-protecting group may be removed from the product compound (I) by a conventional deprotecting technique, for example, by hydrolysis or reduction, and for such a product compound bearing an acyl group as the amino-protecting group to be removed, it is feasible to subject such product compound (I) to a reaction with an imino-halogenating agent and then with an imino-etherifing agent, if necessary, followed by hydrolysis. Acid hydrolysis is one of the conventional methods for removing the amino-protecting groups and is applicable to the removal of such groups as an alkoxycarbonyl group, formyl group and trityl group. The acids available for this acid hydrolysis may be formic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid and other organic or inorganic acids, and preferably the acids are formic acid, trifluoroacetic acid and hydrochloric acid which afford easy after-treatment of the reaction mixture. These acids for hydrolysis are selected properly according to the nature of the amino-protecting group to be removed. This hydrolysis reaction may be carried out either in the absence of any solvent or in the presence of a solvent such as water, a hydrophilic organic solvent or a mixture of organic solvents. When trifluoroacetic acid is employed for the acid hydrolysis, the reaction may suitably be conducted in the presence of anisole.

The carboxyl-protecting group may be removed also in a conventional manner, for example, by hydrolysis or reduction. Acid hydrolysis is one of the conventional deprotection methods which is advantageously applicable to the removal of the carboxyl-protecting group of such kind as silyl group and diphenylmethyl group.

The conversion of the carboxyl group into the metabolically unstable ester group may be performed by a conventional method comprising reacting a metal salt of the corresponding carboxylic acid compound with an alkyl halide such as a pivaloyloxymethyl halide e.g. chloride in an organic solvent.

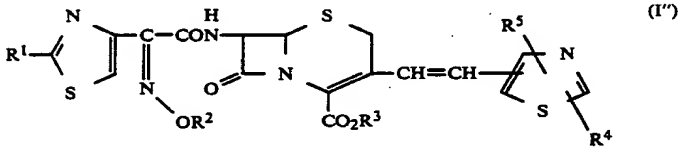
Method 2:

According to this Method 2, such a cephalosporin compound of the formula (I) where the group A denotes a 3-lower-alkylthiazolyl group, that is, such a compound of the following formula (I'):



(I')

wherein R^1, R^2 and R^3 are as defined above, R is a lower alkyl group, and R^4 and R^5 are the same or different and each are a hydrogen atom, a lower alkyl group or a halogen atom such as chlorine atom (which may be prepared by the procedure of the Method 1 above) is produced by the method comprising reacting a compound of the formula (I'')



(I'')

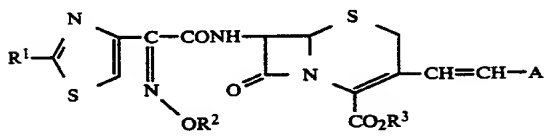
wherein R^1, R^2, R^3, R^4 and R^5 are as defined above, with an alkylating agent selected from an alkyl halide of the formula RX wherein R is a lwer alkyl group such as methyl and ethyl and X is a halogen atom such as chlorine, bromine or iodine atom; a mono- or di-lower-alkyl sulfate; and a lower alkyl lower-alkanesulfonate, to alkylate the 3-nitrogen atom of the thiazolyl group of the compound of the formula (I''). The alkyl halide of the formula RX as the alkylation agent may be methyl bromide, methyl iodide, ethyl bromide and ethyl iodide, for example. The mono-or di-lower-alkyl sulfate as the alkylation agent may be mono-methyl or di-methyl sulfate and mono-ethyl or di-ethyl sulfate. The lower alkyl lower-alkanesulfonate may be methyl methanesulfonate, for example. The reaction of alkylating the 3-nitrogen atom of the thiazolyl group of the compound (I'') may be achieved in a conventional manner known for alkylation of the organic nitrogen atom. When the alkylation reaction is conducted using a lower alkyl ester of the sulfuric or sulfonic acid as the alkylating agent (RX), this reaction may normally be conducted in a solvent such as benzene, toluene, dichloroethane, dichloromethane, chloroform, water, acetone, tetrahydrofurane, ethanol, ethyl ether, dimethylformamide or in any other solvent which exerts no adverse effect on the progress of this reaction.

This reaction according to Method 2 may also preferably be conducted in the presence of such an inorganic or organic base as described in Method 1. The alkyla-

tion reaction as above may be carried out at any temperature which is not limited critically, and the alkylation may usually be conducted at a temperature of up to the boiling point of the solvent used in this reaction, under cooling or heating.

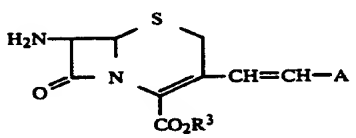
The product compound (I') which has been prepared by the above alkylation reaction may, if desired, then be subjected to further conventional step(s) for removing the remaining carboxyl-protecting group and/or the remaining amino-protecting group therefrom, and/or to further convention step(s) for converting the carboxyl group(s) of the product compound (I') into a metabolically unstable, non-toxic ester (carboxylate) group, in the same manner as described for the procedures of Method 1.

According to a second aspect of this invention, therefore, there is provided a process for the production of a cephalosporin compound of the general formula (I)



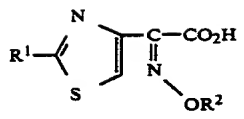
(I)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, and A is an unsubstituted or substituted phenyl group, an unsubstituted or substituted furyl group or an unsubstituted or substituted thiazolyl group or an unsubstituted or substituted 3-lower-alkylthiazolio group, characterized in that the process comprises reacting a 7-aminocephalosporanic acid compound of the general formula (II)



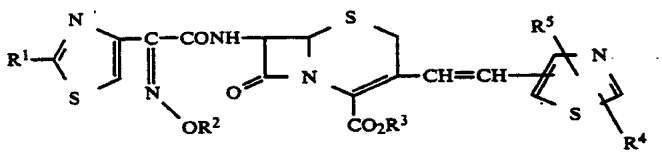
(II)

wherein R^3 and A are as defined above, or a functional equivalent thereof (including a reactive derivative at the amino group of the compound of the formula (II) and a salt of the compound of the formula (II)), with a 2-(2-aminothiazol-4-yl)-2-alkoxyimino-acetic acid compound of the formula (III)



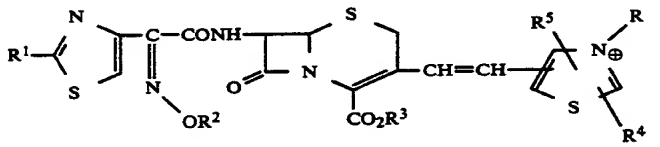
(III)

wherein R^1 and R^2 are as defined above, or a functional equivalent thereof (including a reactive acid derivative of the compound of the formula (III)) in an unreactive solvent at a temperature of not higher than the boiling temperature of the solvent used, to produce the compound of the formula (I), and then, if desired, where the product compound of the formula (I) as produced is such one as shown by the formula (I'')



(I'')

wherein R^1, R^2 and R^3 are as defined above, and R^4 and R^5 are the same or different and each are a hydrogen atom, a lower alkyl group or a halogen atom such as a chlorine atom, alkylating the 3-nitrogen atom of the thiazolyl group of the compound of the formula (I'') by reacting with an alkyl halide of the formula RX wherein R is a lower alkyl group and X is a halogen atom, such as chlorine or bromine atom, or a mono- or di-lower-alkyl sulfate or a lower alkyl lower-alkanesulfonate, to produce the compound of the formula (I''')



(I''')

wherein R^1, R^2, R^3, R^4 and R^5 are as defined above and R is corresponding to the lower alkyl group of the alkyl halide or the mono- or di-lower-alkyl sulfate or the lower alkyl lower-alkanesulfonate employed, and further, if desired, removing the remaining amino-protecting group and the remaining carboxyl-protecting group from the product compound of the formula (I) or of the formula (I''').

The process of the second aspect of this invention may include a further step of reacting the compound of the formula (I) where R^3 is a hydrogen atom, with an alkali metal hydroxide, an alkali metal hydrogen carbonate or an alkali metal carbonate or an alcohol such as a lower alkanol to produce the compound of the formula (I) where R^3 is an alkali metal cation or an ester-forming group such as a lower alkyl group. This reaction may be carried out in a known manner for the conversion of a carboxylic acid into a corresponding alkali metal carboxylate or an ester of the carboxylic acid. In this way, the compound of the formula (I) in the form of a free carboxylic acid may be converted into the form of an alkali metal carboxylate or a carboxylic acid ester.

Examples of the pharmaceutically acceptable salts of the compound of the formula (I) include ordinary non-

toxic salts, for example, salts (carboxylate) with an alkali metal such as sodium and potassium; salts with an alkaline earth metal such as calcium and magnesium; ammonium salt; acid addition salts of the compound (I) with an organic base such as trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine; acid-addition salts of the compound (I) with an organic acid such as acetic acid, trifluoroacetic acid, maleic acid, tartaric acid, methanesulfonic acid, benzenesulfonic acid, formic acid and toluenesulfonic acid; acid-addition salts with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid; acid-addition salts with an amino acid such as arginic acid, aspartic acid and glutamic acid.

Examples of the pharmaceutically acceptable ester of the compound of the formula (I) according to this invention include the esters which are obtained by the esterification of the 2-carboxyl group of the compound of the formula (I) with a lower alkanoyloxymethyl group such as pivaloyloxymethyl group, a lower alkylcarbonyloxyalkyl group, a lower alkoxycarbonyloxyalkyl group, or a (2-oxo-1,3-dioxolene-4-yl)methyl group and the like.

The compounds of this invention are all novel compounds. Minimum inhibitory concentrations (MIC., μg/ml) of some of the new compounds against growth of bacteria as determined by agar-dilution method are shown in Table 1 below. As be apparent from Table 1, all the compounds under test of this invention exhibit high antibacterial activity and a wide range of antibacterial spectra, indicating that the new compounds of this invention are useful as antibacterial agent.

TABLE 1

Test Organisms	MIC. (μg/ml) Example No. Compound 10	11	12	13	14	15	16	18	21	30	31	32	33	34
Staphylococcus aureus 209P JC-1	0.20	0.78	0.39	6.25	0.20	0.78	3.13	0.39	0.10	0.78	0.78	0.39	0.39	0.20
Staphylococcus aureus Smith	0.39	0.78	0.78	6.25	0.39	0.78	3.13	0.39	0.20	1.56	1.56	0.78	0.39	0.20
Escherichia coli NIHJ JC-2	0.39	3.13	3.13	6.25	3.13	0.10	0.39	0.78	0.20	0.78	1.56	1.56	0.39	3.13
Klebsiella pneumoniae PCI 602	0.39	3.13	1.56	3.13	3.13	0.10	0.20	0.39	0.10	0.78	1.56	1.56	0.20	3.13
Proteus mirabilis GN 79	0.39	0.78	0.78	12.5	0.20	0.78	0.05	—	0.20	0.20	0.78	—	0.39	0.78
Proteus vulgaris GN 76	0.20	0.78	0.39	3.13	0.20	0.39	≦0.025	0.10	0.10	0.10	0.20	0.10	0.10	1.56
Proteus rettgeri GN 624	3.13	3.13	3.13	3.13	1.56	0.39	1.56	0.39	1.56	0.20	0.78	6.25	0.78	1.56
Salmonella typhimurium LT-2	0.39	6.25	1.56	6.25	3.13	0.10	0.10	0.78	0.20	0.39	1.56	0.78	0.39	3.13
Serratia marcescens No. 1	0.39	1.56	1.56	6.25	1.56	0.10	0.05	0.39	0.20	0.20	0.78	0.78	0.39	1.56
Pseudomonas aeruginosa MB 3833	25	>50	>50	>50	>50	>50	12.5	50	12.5	>50	>50	100	25	100

Referring to Table 1 above, the Compounds of Examples under test are identified as follows:

Example No. 10 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid trifluoroacetate (cyn-isomer, cis-isomer)

Example No. 11 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-(2-phenylvinyl)-3-cephem-4-carboxylic acid trifluoroacetate (cyn-isomer, cis-isomer)

Example No. 12 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-furyl)vinyl]-3-cephem-4-carboxylic acid sodium salt (cyn-isomer, cis-isomer).

Example No. 13 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(5-nitor-2-furyl)vinyl]-3-cephem-4-carboxylic acid sodium salt (syn-isomer, trans-isomer).

Example No. 14 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(o-fluorophenyl)vinyl]-3-cephem-4-carboxylic acid trifluoroacetate (syn-isomer, mixed cis- and trans-isomers).

Example No. 15 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(3,4-dimethyl-5-thiazolio)vinyl]-3-cephem-4-carboxylic acid di-trifluoroacetate (syn-isomer).

Example No. 16 Compound:
7-[2-carboxymethoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5yl)vinyl]-3-cephem-4-carboxylic acid trifluoroacetate (syn-isomer, trans-isomer).

Example No. 18 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido-3-[2-(4-methylthiazol-5-yl)vinyl]-3cephem-4-carboxylic acid sodium salt (syn-isomer, trans-isomer).

Example No. 21 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-chlorothazol-5-yl)vinyl]-3-cephem-4-carboxylic acid sodium salt (syn-isomer, cis-isomer).

Example No. 30 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid trifluoroacetate (syn-isomer, trans-isomer).

Example No. 31 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid trifluoroacetate (syn-isomer, cis-isomer).

Example No. 32 Compound:
7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-4-yl)vinyl]-3-cephem-4-carboxylic acid sodium salt (syn-isomer, cis-isomer).

Example No. 33 Compound:

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid sodium salt (syn-isomer, cis-isomer).

Example No. 34 Compound:

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2,4-dichlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid sodium salt (syn-isomer, cis-isomer).

The new compound of the formula (I) or the formula (Ia) to (If) according to this invention, or a pharmaceutically acceptable salt or ester thereof may be formulated into a pharmaceutical composition by mixing with a pharmaceutically acceptable solid or liquid carrier or vehicle when it is to be administered to man for the therapeutic treatment of bacterial infections.

According to a further aspect of this invention, therefore, there is provided a pharmaceutical, antibacterial composition which comprises an antibacterially effective amount of the compound of the fromula (I) or of the formula (Ia) to (If) as defined hereinbefore or a pharmaceutically acceptable salt or ester thereof as the active ingredient, in combination of a pharmaceutically acceptable carrier for the active ingredient.

The pharmaceutically acceptable carrier as mixed with the active ingredient compound may be an ordinary solid or liquid one, either organic or inorganic, which may be chosen appropriately depending on whether the pharmaceutical formulation as prepared is to be administered orally or non-orally or applied externally. The pharmaceutical composition of this invention may be of any conventional formulation form such as capsules, tablets, sugar-coated pills, ointment, suppository, solution, suspension and emulsion. Other conventional additives, including adjuvant, stabilizing agent, wetting agent, emulsifying agent, buffer solution may also be incorporated into the pharmaceutical composition of this invention containing the compound (I) as the active ingredient.

The new cephalosporin compound of this invention as orally administered is easily absorbed through the intestines by a living animal and maintains its antibacterial activity to a substantial extent in the body of the animal until it is excreted in the urine of the animal, and this may be observed by determining the remaining amount of the cephalosporin compound of this invention which can be recovered in the urine without receiving a substantial degradation of the compound in vivo. Some tests were made to evaluate the amount of the cephalosporin compound of this invention which can be recovered as the antibacterially active compound from the urine after it was orally given to mice.

Test 1

To mice of ICR-strain (male, 4-weeks-aged, three in each group) was orally administered the compound under test identified below, at a dosage of the compound of 0.5 mg per mouse. The compound under test was given as a suspension of the test compound in a solution of 0.2% carboxymethylcellulose (CMC) in water. By the end of 4 hours after the administration of the test compound, all the amounts of the urine excreted by the treated mice were collected together, and the total quantity of the cephalosporin compound of this invention (as the free carboxylic acid form) in the urine was determined according to a paper-disc assay method using *Escherichia coli* K-12 8236 as the assaying strain.

The compound under test was the Example No. 22 Compound, namely 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) pivaloyloxymethyl ester; and the Example No. 38 Compound, namely 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetoamido]-3-[2-(thiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (cyn-isomer, cis-isomer) pivaloyloxymethyl ester.

Rate of recovery of the cephalosporin compound in urine was calculated in term of percentages of the molar quantity of the cephalosporin compound as recovered (as the free carboxylic acid form) based on the molar quanitity of the cephalosporin compound as orally given.

The test results obtained (as averaged for three mice) are shown in Table 2 below.

TABLE 2

Test compound	Rate of recovery of the test compound in urine (%)
Example No. 22 Compound	24
Example No. 38 Compound	20

In the above tests, the cephalosporin compounds under test as orally given each were converted in vivo into the corresponding free carboxylic acid form owing to easy cleavage of the ester-forming pivaloyloxymethyl group from the 4-carboxyl group of the compound after they were absorbed in the animal body. The test compounds were excreted in the urine in the form of its free carboxylic acid, of which the antibacterial potency was evaluated by the bio-assay method.

This invention is now illustrated with reference to the following Examples. Examples 1–39 illustrate the procedures for preparing the new cephalosporin compounds of this invention, and Reference Examples 1–8 illustrate the procedures for preparing the starting compounds employed for the preparation of the new compounds of this invention.

REFERENCE EXAMPLE 1

Production of 7-(phenoxyacetamido)-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid benzhydryl ester

(1) Benzhydryl 7-(phenoxyacetamido)-3-(triphenylphosphoran-diylmethyl)-3-cephem-4-carboxylate (1.55 g) and 4-methylthiazol-5-carboaldehyde (0.305 g) were dissolved in methylene chloride (20 ml), to which aqueous saturated sodium bicarbonate (20 ml) was added at ambient temperature. The resultant mixture was stirred for 17 hours at ambient temperature. The mixture was allowed to stand until it separated into the aqueous phase and organic solvent phase. The aqueous phase was removed and washed with methylene chloride (20 ml), and the washings (in methylene chloride) were combined with the organic solvent phase separated. The combined solution was dried over anhydrous magnesium sulfate and then concentrated to dryness under reduced pressure. The solid residue obtained was purified chromatographically on a column of silica gel (Wako gel C-300) (40 g) as developed with benzene-ethyl acetate (5:1) as the development solvent. The entitled compound, 7-(phenoxyacetamido)-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid benzhydryl ester (0.741 g) was obtained.

NMR, δ ($CDCl_3$): 2.34 (3H, s), 3.24 (1H, d, J=18 Hz), 3.48 (1H, d, J=18 Hz), 4.55 (2H, s), 5.12 (1H, d, J=5 Hz), 5.95 (1H, dd, J=5 Hz, 9 Hz), 6.25 (1H, d,

J=12 Hz), 6.49 (1H, d, J=12 Hz), 6.8–7.5 (16H, m), 8.56 (1H, s).

(2) Benzhydryl 7-(phenoxyacetamido)-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylate (0.725 g) was dissolved in anisole (2 ml), to which trifluoroacetic acid (7 ml) was added under ice-cooling. The mixture was stirred for 1 hour under ice-cooling. The reaction mixture was concentrated under reduced pressure to give a syrup, whcih was then solidified by addition of isopropyl ether thereto. The solid obtained was pulverized and was mixed with isopropyl ether for the washing purpose, and the mixture was filtered to recover the solid which was then dried under reduced presssure. 7-(Phenoxyacetamido)-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (0.512 g) was thus obtained.

NMR, δ ($CDCl_3$): 2.38 (3H, s), 3.19 (1H, d, J=18 Hz), 3.46 (1H, d, J=18 Hz), 4.55 (2H, s) 5.09 (1H, d, J=5 Hz), 5.91 (1H, d, J=5 Hz), 6.44 (1H, d, J=12 Hz), 6.57 (1H, d, J=12 Hz), 6.8–7.6 (6H, m), 8.79 (1H, s).

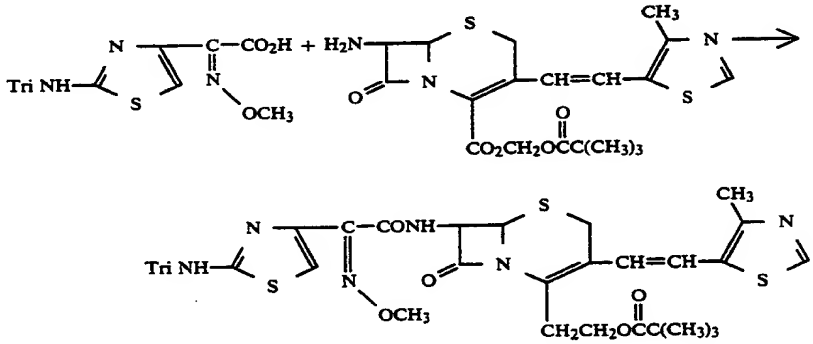
(3) 7-(Phenoxyacetamido)-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (0.490 g) was dissolved in ethyl acetate (5 ml), to which sodium 2-ethylhexanoate (0.300 g) was added. The resultant mixture was stirred for 30 minutes, and the precipitate as formed was removed from the mixture by filtration and washed with a mixture of ethyl acetate and isopropyl ether (1:1). The solid product (as the sodium salt) was dissolved in dimethylformamide (5 ml) under ice-cooling, to which was added such a solution in dimethylformamide (3 ml) of iodomethyl pivalate as prepared from chloromethyl pivalate (0.450 g) and sodium iodide (0.450 g). The resultant mixture was stirred for 1 hour under ice-cooling. To the reaction mixture was added ethyl acetate (50 ml), followed by washing the mixture three times with ice-water (each 30 ml). The organic solvent phase was separated out of the mixture, dried over anhydrous magnesium sulfate and then concentrated to dryness under reduced pressure. The solid residue obtained was purified chromatographically on a column of silica gel (Wako-gel C-300) (20 g) as developed with benzene-ethyl acetate (5:1) as the development solvent. 7-(Phenoxyacetamido)-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester (0.405 g) was thus obtained.

NMR, δ ($CDCl_3$): 1.15 (9H, s), 2.45 (3H, s), 3.17 (1H, d, J=18 Hz), 3.50 (1H, d, J=18 Hz), 4.57 (2H, s), 5.12 (1H, d, J=5 Hz), 5.77 (1H, d, J=5 Hz), 5.84 (1H, d, J=5 Hz), 5.95 (1H, dd, J=5 Hz, 9 Hz), 6.35 (1H, d, J=12 Hz), 6.64 (1H, d, J=12 Hz), 6.8–7.5 (6H, m), 8.62 (1H, s).

(4) 7-(Phenoxyacetamido)-3-[2-(4-methylthiazol-5yl vinyl]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester (0.303 g) was dissolved in methylene chloride (3 ml). The solution obtained was poured into a solution (10 ml) containing phosphorus pentachloride (0.331 g) and pyridine (0.43 g) in methylene chloride at −30° C. The resultant solution was stirred for 3 hours under ice-cooling and was poured into methanol (20 ml) as cooled previously to −30° C., followed by stirring the mixture for further 30 minutes at ambient temperature. The reaction solution obtainedd was then poured into a mixture of aqueous saturated sodium chloride (50 ml) and methylene chloride (50 ml) under ice-cooling, followed by stirring for 1 hour under ice-cooling. The organic phase was separated from the aqueous phase, and the aqueous phase was extracted with methylene chloride (20 ml). The extract (in methylene chloride) was combined with said organic phase, and the resultant mixture was washed with aqueous saturated sodium bicarbonate solution. The washed organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a volume of 5 ml. 7-Amino-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester was thus obtained as its solution in methylene chloride.

EXAMPLE 1

Production of 7-[2methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) pivaloyloxymethyl ester



(Tri denotes trityl group.)

7-Amino-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester (0.229 g) as prepared in Reference Example 1 above was dissolved in methylene chloride (5 ml). The resultant solution was admixed with 2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetic acid (syn-isomer) (0.235 g) and methylene chloride (5 ml). To the mixture obtained were further added pyridine (0.07 ml) and then dropwise phosphorus oxychloride (0.07 ml) at −20° C. The reaction mixture was stirred for 10 minutes at 0° C. and poured into a mixture of ice-water (50 ml) and ethyl acetate (50 ml). After stirring, the organic phase was separated from the aqueous phase and washed with ice-wated and then with ice-cooled aqueous saturated sodium hydrogen carbonate solution. The organic phase was dried over

anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified chromatographically on a column of silica gel (Wako gel C-300) (20 g) as developed with benzene-ethyl acetate (5:1) as the development solvent. 7-[2-Methoxyimino-2(2-tritylaminothiazol-4yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) pivaloyloxymethyl ester (0.184 g) was obtained.

NMR, δ ($CDCl_3$): 1.13 (9H, s), 2.43 (3H, s), 3.26 (1H, d, J=18 Hz), 3.57 (1H, d, J=18 Hz), 4.04 (3H, s), 5.13 (1H, d, J=5 Hz), 5.76 (1H, d, J=5 Hz), 5.82 (1H, d, J=5 Hz), 5.95 (1H, dd, J=5 Hz, 9 Hz), 6.34 (1H, d, J=12 Hz), 6.64 (1H, d, J=12 Hz), 6.70 (1H, s), 6.90 (1H, d, J=9 Hz), 7.00 (1H, broad s), 7.1–7.5 (25H, m), 8.59 (1H, s).

EXAMPLE 2

Production of 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) pivaloyloxymethyl ester

7-[2-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) pivaloyloxymethyl ester (0.160 g) was dissolved in anisole (0.5 ml). The resultant solution was admixed with trifluoroacetic acid (1.15 ml) under ice-cooling, followed by stirring for 30 minutes again under ice-cooling. The reaction solution was mixed with isopropyl ether (30 ml), and the powder substance deposited was recovered by filtration and washed with isopropyl ether. The solid obtained was dissolved in ethyl acetate (20 ml), washed with ice-coole aqueous saturated sodium hydrogen carbonate solution (10 ml). The organic phase was separated from the aqueous phase, dried over anhydrous sodium sulfate and concentrated under reduced pressure. 7-[2-Methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) pivaloyloxymethyl ester (0.083) was thus obtained.

NMR, δ ($CDCl_3$): 1.14 (9H, s), 2.44 (3H, s), 3.30 (1H, d, J=18 Hz), 3.47 (1H, d, J=18 Hz), 4.04 (3H, s), 5.17 (1H, d, J=5 Hz), 5.27 (2H, b), 5.77 (1H, d, J=5 Hz), 5.82 (1H, d, J=5 Hz), 6.03 (1H, dd, J=5 Hz, 9 Hz), 6.35 (1H, d, J=12 Hz), 6.64 (1H, d, J=12 Hz), 6.88 (1H, s), 7.35 (1H, d, J=9 Hz), 8.59 1H, s).

EXAMPLE 3

7-Amino-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid benzhydryl ester (0.223 g) and 2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetic acid (0.252 g) were reacted with each other and the reaction product was processed in the same manner as in Example 1, to obtain 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamide]-3-[2-(4-methylthizol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) benzhydryl ester (0.215 g).

NMR, δ ($CDCl_3$): 2.35 (3H, d, J=18 Hz), 3.45 (1H, d, J=18 Hz), 4.05 (3H, s), 5.14 (1H, d, J=5 Hz), 5.98 (1H, dd, J=5 Hz, 9 Hz), 6.27 (1H, d, J=12 Hz), 6.45 (1H, d, J=12 Hz), 6.72 (1H, s), 6.88 (1H, s), 6.99 (1H, broad s), 7.10–7.5 (26H, m), (1H, s).

EXAMPLES 4–8

The following compounds were produced in the same manner as in Example 1:

EXAMPLE 4

7-[2-Methoxyimino-2-(tritylaminothiazol-4-yl)acetamido]-3-(2-phenylvinyl)-3-cephem-4-carboxylic acid (syn-isomer) benzhydryl ester (yield 68%).

NMR, δ ($CDCl_3$): 3.25 (2H, broad s), 4.04 (3H, s), 5.05 (1H, d, J=5 Hz), 5.91 (1H, d, J=5 Hz), 6.48 (1H, d, J=12 Hz), 6.60 (1H, d, J=12 Hz), 6.74 (1H, s), 6.95 (1H, s), 7.0–7.5 C32H, m).

EXAMPLE 5

7-[2-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) benzhydryl ester (yield 62%).

NMR, δ ($CDCl_3$): 3.50 (2H, broad s), 4.07 (3H, s), 5.11 ((1H, d, J=5 Hz), 5.91 (1H, dd, J=5 Hz, 9 Hz), 6.1–6.4 (4H, m), 6.76 (1H, s), 7.00 (1H, broad s), 7.1–7.6 (27H, m).

EXAMPLE 6

7-[2-(Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(5-nitro-2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) benzhydryl ester (yield 75%).

NMR, δ ($CDCl_3$): 3.40 (1H, d, J=18 Hz), 3.63 (1H, d, J=18 Hz), 4.10 (3H, s), 5.32 (1H, d, J=5 Hz), 6.05 (1H, dd, J=5 Hz, 9 Hz), (1H, d, J=12 Hz), 6.31 (1H, d, J=4 Hz), 6.53 (1H, d, J=12 Hz), 6.78 (1H, s), 6.86 (1H, s), 7.00 (1H, broad s), 7.13 (1H, d, J=4 Hz), 7.15–7.5 (26H, m).

EXAMPLE 7

7-2-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(o-fluorophenyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) benzhydryl ester (yield 71%).

NMR, δ ($CDCl_3$): 3.23 (2H, broad s), 4.02 (3H, s), 5.03 (1H, d, J=5 Hz), 5.91 (1H, dd, J=5 Hz, 9 Hz), 6.57 (1H, d, J=12 Hz), 6.63 (1H, d, J=12 Hz), 6.72 (1H, s), 6.93 (1H, s), 6.95–7.5 (31H, n).

EXAMPLE 8

7-[2-t-Butoxycarbonylmethoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) benzhydryl ester (yiled 81%).

NMR, δ ($CDCl_3$): 1.43 (9H, s) 2.36 (3H, s), 3.25 (1H, d, J=18 Hz), 3.55 (1H, d, J=18 Hz), 4.75 (2H, S), 5.14 (1H, d, J=5 Hz), 5.94 (1H, dd, J=5 Hz, 9 Hz), 6.27 (1H, d, J=12 Hz), 6.45 (1H, d, J=12 Hz), 6.80 (1H, s), 6.86 (1H, s), 6.99 (1H, broad s), 7.1–7.5 (25H, m), 8.53 (1H, s), 8.56 (1H, d, J=9 Hz).

EXAMPLE 9

Production of 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(3,4-dimethyl-5-thiazolio)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) benzhydryl ester iodide

7-[2-Methoxyimino-2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid benzhydroyl ester (0.164 mg) was dissolved in benzene (5 ml), to which was added methyl iodide (1 ml). The solution so obtained was stirred for 7 days so that a precipitate was deposited. The precipitate was removed by filtration, washed with benzene and dried under reduced pressure, to afford 7-[2-methox-

yimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(3,4-dimethyl-5-thiazolio)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) benzhydryl ester iodide (0.122 mg).

NMR, δ ($CDCl_3$): 2.30 (3H, s), 3.32 (1H, d, J=18 Hz), 3.65 (1H, d, J=18 Hz), 4.02 (3H, s), 4.06 (3H, s), 5.42 (1H, d, J=5 Hz), 5.92 (1H, dd, J=5 Hz, 9 Hz), 6.29 (1H, d, J=12 Hz), 6.56 (1H, d, J=12 Hz), 6.64 (1H, s), 6.89 (1H, s), 7.0–7.5 (27H, m) 10.19 (1H, s).

EXAMPLE 10

Production of 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) trifluoroacetate

7-[2-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid benzhydryl ester (0.11 g) was dissolved in anisole (0.33 mg), to which was added trifluoroacetic acid (1.1 ml) under ice-cooling. The solution so obtained was stirred for 1 hour under ice-cooling and the reaction solution was admixed with isopropyl ether (30 ml) to deposit a precipitate. The precipitate was recovered by filtration, washed with isopropyl ether and dried under reduced pressure. 7-[2-Methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) trifluoroacetate (0.067 g) was obtained.

NMR, δ (CD_3SOCD_3): 2.44 (3H, s), 3.39 (1H, d, J=18 Hz), 3.46 (1H, d, J=18 Hz), 3.84 (3H, s), 5.22 (1H, d, J=5 Hz), 5.80 (1H, dd, J=5 Hz, 9 Hz), 6.36 (1H, d, J=12 Hz), 6.67 (1H, d, J=12 Hz), 6.76 (1H, s), 8.90 (1H, s), 9.63 (1H, d, J=9 Hz).

EXAMPLE 11–16

The following compounds were prepared in the same manner as in Example 10.

Sodium salt of the compounds of Examples 12 and 13 given below were produced by preparing the trifluoroacetate of the corresponding compounds in the same manner as in Example 10, dissolving said trifluoroacetate in an aqueous solution of 2 molar equivalents of sodium hydrogen carbonate, purifying chromatographically the resulting solution on a column of Diaion HP20 (100-fold volume) as eluted with water and aqueous 20% acetone, and freeze-drying the eluate containing the desired compound.

EXAMPLE 11

7-[2-Methoxyimino-2-aminothiazol-4-yl)acetamido]-3-(2-phenylvinyl)-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) trifluoroacetate (yield 79%).

NMR, δ (CD_3DOCD_3): 3.17 (1H, d, J=18 Hz), 3.42 (1H, d, J=18 Hz), 3.82 (3H, s), 5.20 (1H, d, J=5 Hz), 5.76 (1H, dd, J=5 Hz, 9 Hz), 6.52 (1H, d, J=12 Hz), 6.58 (1H, d, J=12 Hz), 6.73 (1H, s), 7.1–7.5 (5H, m), 9.57 (1H, d, J=9 Hz).

EXAMPLE 12

7-[2-Methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) sodium salt (yield 13%).

NMR, δ (D_2O): 3.51 (1H, d, J=18 Hz), 3.72 (1H, d, J=18 Hz), 4.03 (3H, s), 5.39 (1H, d, J=5 Hz), 5.86 (1H, d, J=5 Hz), 6.22 (1H, d, J=12 Hz), 6.44 (1H, d, J=12 Hz), 6.4–6.6 (2H, m), 7.07 (1H, s) 7.54 (1H, d, J=2 Hz).

EXAMPLE 13

7-[2-Methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(5-nitor-2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer) sodium salt (yield 53%).

NMR, δ (D_2O): 3.57 (1H, d, J=18 Hz), 3.82 (1H, d, J=18 Hz), 4.03 (3H, s), 5.34 (1H, d, J=5 Hz), 5.88 (1H, d, J=5 Hz), 6.76 (1H, d, J=15 Hz), 6.79 (1H, d, J=4 Hz), 7.05 (1H, s) 7.46 (1H, d, J=15 Hz), 7.60 (1H, d, J=4 Hz).

EXAMPLE 14

7-[2-Methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(o-fluorophenyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, mixed cis- and trans-isomers) trifluoroacetate (yield 84%).

NMR, δ (CD_3SOCD_3): 3.12 (1H, d, J=18 Hz), 3.33 (1H, d, J=18 Hz), 3.77 (3H, s), 5.07 (1H, d, J=5 Hz), 5.65 (1H, dd, J=5 Hz, 9 Hz), 6.47 (2H, s), 6.63 (1H, s), 6.9–7.5 (4H, m), 9.42 (1H, d, J=9 Hz).

EXAMPLE 15

7[2-Methoxyimino-2-(2-aminothiazol-4-yl)acetamido-3-[2-(3,4-dimethyl-5-thiazolio)vinyl]-3-cephem-4-carboxylic acid (syn-isomer) di-trifluoroacetate (yield 73%).

NMR, δ (CH_3SOCD_3): 2.42 (3H, s), 3.37 (1H, d, J=18 Hz), 3.52 (1H, d, J=18 Hz), 3.82 (3H, s), 4.04 (3H, s), 5.24 (d, J=5 Hz), 5.80 (1H, dd, J=5 Hz, 9 Hz), 6.72 (3H, s), 9.56 (1H, d, J=9 Hz), 10.25 (1H, s).

EXAMPLE 16

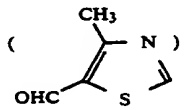
7-[2-Carboxymethoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol)-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer) trifluoroacetate (yield 58%).

NMR, δ (CD_3SOCD_3): 2.37 (3H, s), 3.36 (1H, d, J=18 Hz), 3.51 (1H, d, J=18 Hz), 4.62 (2H, s), 5.27 (1H, d, J=5 Hz), 5.87 (1H, dd, J=5 Hz, 9 Hz), 6.37 (1H, d, J=12 Hz), 6.83 (1H, s), 8.93 (1H, s), 9.62 (1H, d, J=9 Hz).

REFERENCE EXAMPLE 2

Production of 7-amino-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (trans-isomer) p-methoxybenzyl ester

(1) p-Methoxybenzyl 7-phenylacetamido-3-chloromethyl-3-cephem-3-carboxylate (10.00 g, 20.52 mmol) and triphenylphosphine (5.65 g, 21.5 mmol) were dissolved in acetone (200 ml), to which sodium iodide (3.23 g, 21.5 mmol) was added at ambient temperature. The resultant mixture was stirred for 2 hours and concentrated to dryness under reduced pressure. To the solid residue were added methylene chloride (100 ml), 4-methylthiazol-5-yl-carboaldehyde



(26.07 g, 20.5 mmol) and aqueous saturated sodium hydrogen carbonate solution (100 ml) successively, followed by stirring the resultant mixture for 16 hours at ambient temperture. The mixture obtained was al-

lowed to stand until it separated into the aqueous phase and organic solvent phase. The organic phase was separated from the aqueous phase, and washed with aqueous 10% sodium bisulfite solution (250 ml) and then with aqueous saturated sodium chloride solution (250 ml). The organic phase as washed was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. To the residue was added methanol (200 ml) to deposit a precipitate which was then filtered out, washed with methanol and dried under reduced pressure. 7-Phenylacetamido-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (trans-isomer) p-methoxybenzyl ester was thus obtained as a light yellow colored powder (yield 1.20 g, 10%).

NMR, δ ($CDCl_3$): 2.40 (3H, s), 3.60 (2H, broad s), 3.62 (2H, s), 3.78 (3H, s), 4.93 (1H, d, J=5 Hz), 5.20 (2H, s), 5.79 (dd, J=5 Hz, 9 Hz), 6.6–6.9 (4H, m), 7.0–7.4 (8H, m), 8.51 (1H, s).

(2) p-Methoxybenzyl 7-phenylacetamido-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylate (trans-isomer) (0.720 g, 1.28 mmol) was dissolved in methylene chloride (3 ml). The resultant solution was poured into a solution of phosphorus pentachloride (0.800 g, 3.84 mmol) and pyridine (1.04 ml, 12.8 mmol) in methylene chloride (20 ml) at −30° C. The resultant solution was stirred for 3 hours under ice-cooling and poured into methanol (20 ml) as pre-cooled to −30° C., followed by stirring the mixture for 1 hour at ambient temperature. The reaction solution obtained was poured into a mixture of aqueous saturated sodium chloride solution (20 ml) and methylene chloride (20 ml), and the resulting mixture was stirred for 1 hour. The mixture was cooled to stand until it separated into the aqueous phase and organic solvent phase. The aqueous phase separated out was extracted with methylene chloride (20 ml) and the methylene chloride extract was combined with the organic phase mentioned above. The combined organic phase was washed with aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue obtained was purified chromatographically on a column of silica gel (Wako gel C-300) (20 g) as developed with benzene-ethyl acetate (3:1) as the development solvent. The titled compound, 7-amino-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (trans-isomer) p-methoxybenzyl ester (0.443 g, 78%) was obtained.

NMR, δ ($CDCl_3$): 1.83 (1H, broad s), 2.46 (1H, s), 3.63 (1H, d, J=18 Hz), 3.71 (1H, d, J=18 Hz), 3.77 (3H, s), 4.72 (1H, d, J=5 Hz), 4.94 (1H, d, J=5 Hz), 5.23 (2H, s), 6.85 (1H, d, J=16 Hz), 6.8–6.9 (2H, m), 7.22 (1H, d, J=16 Hz), 7.3–7.4 (2H, m), 8.52 (1H, s).

EXAMPLE 17

Production of 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid p-methoxybenzyl ester (syn-isomer, trans-isomer)

p-Methoxybenzyl 7-amino-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylate (trans-isomer) as prepared by the method of Reference Example 2 as above and 2-(tritylaminothiazol-4-yl)-2-methoxyiminoacetic acid (syn-isomer) were reacted with each other and the reaction product was processed in the same manner as in Example 1 to give the titled compound in a yield of 72%.

NMR, δ ($CDCl_3$): 2.42 (3H, s), 3.57 (1H, d, J=18 Hz), 3.67 (1H, d, J=18 Hz), 3.73 (3H, s), 4.02 (3H, s), 5.01 (1H, d, J=5 Hz), 5.17 (2H, s), 5.84 (1H, dd, J=5 Hz, 9 Hz), 6.63 (1H, s), 6.83 (1H, d, J=16 Hz), 6.8–7.5 (20H, m), 8.49 (1H, s).

EXAMPLE 18

Production of 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid sodium salt (syn-isomer, trans-isomer)

p-Methoxybenzyl 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylate (syn-isomer, trans-isomer) was treated with trifluoroacetic acid and processed in the same manner as in Example 10 to give a trifluoroacetate of the entitled compound (as the carboxylic acid). This trifluoroacetate obtained was dissolved in aqueous sodium hydrogen carbonate solution for neutralization and then purified chromatographically on a column of Diaion HP20 (100 fold-volume) as eluted with water and aqueous 20% acetone. The eluate containing the titled compound was lyophilized to afford the titled compound in a yield of 82%.

NMR, δ (D_2O): 2.50 (3H, s), 3.86 (2H, broad s), 4.06 (3H, s), 5.34 (1H, d, J=5 Hz), 5.87 (1H, d, J=5 Hz), 6.97 (1H, d, J=16 Hz), 7.06 (1H, d, J=16 Hz), 7.08 (1H, s), 8.77 (1H, s).

EXAMPLE 19

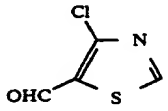
Production of 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester (syn-isomer, trans-isomer)

7-[2-Methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid sodium salt (syn-isomer, trans-isomer) (0.03 g, 0.06 mmol) was dissolved in dimethylformamide (3 ml). To the resultant solution was added a solution in dimethylformamide (1 ml) of iodomethyl pivalate (as prepared by reacting chloromethyl pivalate (0.090 g, 0.60 mmol) with sodium iodide (0.090 g, 0.06 mmol) in acetone) under ice-cooling, followed by stirring the resultant mixture for 10 minutes. The reaction solution as obtained were admixed with ice-water (20 ml) and ethyl acetate (20 ml), stirred thoroughly and then allowed to stand until the mixture separated into aqueous phase and organic phase. The organic phase was separated from the aqueous phase and washed twice with water (10 ml) and then with aqueous saturated NaCl solution (10 ml). The organic phase as washed was subsequently dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified chromatographically on a column of silica-gel (Wako-gel C-300) (5 g) as developed with ethyl acetate. The titled compound was thus obtained (yield 0.025 g, 67%).

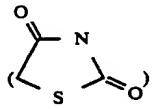
NMR, δ ($CDCl_3$): 1.21 (9H, s), 2.48 (3H, s), 3.68 (1H, d, J=18 Hz), 3.78 (1H, d, J=18 Hz), 4.04 (3H, s), 5.12 (1H, d, J=5 Hz), 5.89 (2H, s), 5.97 (1H, dd, J=5 Hz, 9 Hz), 6.86 (1H, s), 6.98 (1H, d, J=16 Hz), 7.33 (1H, d, J=16 Hz), 7.52 (1H, d, J=9 Hz), 8.57 (1H, s).

REFERENCE EXAMPLE 3

Production of 4-chloro-thiazol-5-yl-carboaldehyde of the formula



Phosphorus oxychloride (122.7 g) was added dropwise to dimethylformamide (73.1 g) under ice-cooling, and the mixture obtained was stirred for 30 minutes (for preparation of Vilsmeier reagent). The mixture was then admixed with thiazoline-2,4-dione



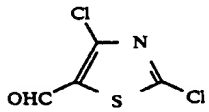
(23.4 g), followed by heating at 100° C. for 3 hours. The reaction solution was cooled to ambient temperature, poured onto ice (200 g), neutralized by addition of sodium acetate and then extracted 4 times with 200 ml-portions of methylene chloride. The resultant extract in methylene chloride was washed with a small volume of saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue obtained was purified chromatographically on a column of silica gel as developed with benzene-ethyl acetate (10:1) as eluent. The titled compound (1.10 g) was obtained as light yellow colored crystals.

NMR, δ ($CDCl_3$): 8.93 (1H, d, J=1 Hz), 10.03 (1H, d, J=1 Hz).

MS (m/e): 148 ($M^+ + 1$)

REFERENCE EXAMPLE 4

Production of 2,4-dichloro-thiazol-4-yl-carboaldehyde of the formula



To a solution of dimethylformamide (73.1 g) in dichloroethylene (200 ml) was added dropwise phosphorus oxychloride (122.7 g) under ice-cooling, followed by stirring for 30 minutes (for preparation of Vilsmeier reagent). The resultant solution was admixed with thiazolin-2,4-dione (23.4 g) and heated for 1 hour under refluxing. The reaction solution obtained was cooled to ambient temperature, poured onto ice (200 g), neutralized by addition of sodium acetate and then extracted 3 times with 200 ml-portions of methylene chloride. The resultant extract in methylene chloride was washed with a small volume of saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue obtained was purified chromatographically on a column of silica-gel as developed with benzene-ethyl acetate (10:1) as eluent. 4-Chloro-thiazol-5-yl-carboaldehyde (0.34 g) was afforded, and the titled compound (2.05 g) was also obtained as light yellow colored crystals.

NMR, δ ($CDCl_3$) : 9.90 (1H, s)

MS (m/e) : 182 ($M^+ + 1$)

REFERENCE EXAMPLE 5

Production of 7-phenylacetamido-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (cis-isomer) p-methoxybenzyl ester

p-Methoxybenzyl 7-phenylacetamido-3-chloromethyl-3-cephem-4-carboxylate (3.265 g, 6.71 mmol) and triphenylphosphine (1.859 g, 7.05 mmol) were dissolved in dimethylformamide (20 ml). The resultant solution was admixed with sodium iodide (1.056 g, 7.05 mmol) at ambient temperature and stirred for 2 hours. The reaction solution obtained was concentrated to dryness under reduced pressure, and the residue was taken up into methylene chloride (10 ml). To the resultant solution in methylene chloride were added 4-chloro-thiazol-5-yl-carboaldehyde (1.100 g) which was obtained in Reference Example 3 described hereinbefore, and then saturated aqueous sodium hydrogen carbonate (10 ml). The mixture obtained was stirred for 6 hours at ambient temperature and then was left until it separated into the aqueous phase and organic phase. The aqueous phase as separated was extracted with methylene chloride (10 ml). The extract in methylene chloride and the organic solvent phase were combined together, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue obtained was purified by flash-column chromatography on a column of silica-gel (Wako-gel C-300) as developed with benzene-ethyl acetate (5:1) as eluent solvent. The titled compound was obtained (yield 2.891 g, 74%).

NMR, δ ($CDCl_3$): 3.15 (1H, d, J=18 Hz), 3.42 (1H, d=18 Hz), 3.61 (2H, s), 3.74 (3H, s), 5.00 (1H, d, J=5 Hz), 5.06 (2H, s), 5.84 (1H, dd, J=5 Hz, 9 Hz), 6.14 (1H, d, J=9 Hz), 6.27 (1H, d, J=12 Hz), 6.56 (1H, d, J=12 Hz), 6.7–6.75 (2H, m), 7.05–7.4 (7H, m), 8.50 (1H, s).

REFERENCE EXAMPLE 6

Production of 7-amino-3-[2-(4-chlorothiazol-5-yl) vinyl]-3-cephem-4-carboxylic acid (cis-isomer) p-methyoxybenzyl ester

p-Methoxybenzyl 7-phenylacetamido-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (cis-isomer) (2.452 g, 4.21 mmol) as prepared in the above Reference Example 5 was dissolved in methylene chloride (10 ml). The resultant solution was poured into a solution of phosphorus pentachloride (2.630 g, 12.63 mmol) and pyridine (3.4 ml, 42 mmol) in methylene chloride (40 ml) at −30° C. under cooling. The reaction solution obtained was stirred for 3 hours under ice-cooling and poured into methanol (40 ml) as pre-cooled to −30° C., followed by stirring the resultant mixture for 1 hour at ambient temperature. The mixture was then added into a mixture of saturated aqueous sodium chloride (100 ml) and methylene chloride (100 ml) and stirred for 1 hour. The mixture obtained was left until it separated into the aqueous phase and organic solvent phase. The aqueous phase was separated and extracted with methylene chloride (50 ml). The extract in methylene chloride was added to the above organic solvent phase, which was then washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue ob-

tained was purified by flash-column chromatography on a column of silica-gel (Wako-gel C-300) as developed with benzene-ethyl acetate (3:1) as eluent. The titled compound was obtained (yield 1.543 g, 79%).

NMR, δ ($CDCl_3$): 1.75 (2H, broad s), 3.20 (1H, d, J=18 Hz), 3.44 (1H, d, J=18 Hz), 3.75 (3H, s), 4.77 (1H, d, J=5 Hz), 4.97 (1H, d, J=5 Hz), 5.08 (2H, s), 6.31 (1H, d, J=12 Hz), 6.53 (1H, d, J=12 Hz), 6.7–6.85 (2H, m), 7.1–7.25 (2H, m), 8.50 (1H, s).

REFERENCE EXAMPLE 7

Production of 7-phenylacetamido-3-[2-(2,4-dichlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (cis-isomer) p-methoxybenzyl ester

p-Methoxybenzyl 7-phenylacetamido-3-chloromethyl-3-cephem-4-carboxylate was reacted with 2,4-dichloro-thiazol-5-yl-carboaldehyde as obtained in the Reference Example 4, in the same manner as in the Reference Example 5. The titled compound was produced in a yield of 78%.

NMR, δ ($CDCl_3$): 3.19 (1H, d, J=18 Hz), 3.40 (1H, d, J=18 Hz), 5.01 (1H, d, J=5 Hz), 5.09 (2H, s), 5.88 (1H, dd, J=5 Hz, 9 Hz), 6.10 (1H, d, J=9Hz), 6.22 (1H, d, J=12 Hz), 6.46 (1H, d, J=12 Hz), 7.7–7.85 (2H, m), 7.1–7.45 (7H, m).

REFERENCE EXAMPLE 8

Production of 7-amino-3-[2-(2,4-dichlorothiazol-5-yl vinyl]-3-cephem-4-carboxylic acid (cis-isomer) p-methoxybenzyl ester

p-Methoxybenzyl 7-phenylacetamido-3-[2-(2,4-dichlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylate (cis-isomer) was treated with phosphorus pentachloride and pyridine in the same manner as in the Reference Example 6 to afford the titled compound in a yield of 73%.

NMR, δ ($CDCl_3$): 1.80 (2H, broad s), 3.20 (1H, d, J=18 Hz), 3.42 (1H, d, J=18 Hz), 3.75 (3H, s), 4.79 (1H, d, J=5 Hz), 4.98 (1H, d, J=5 Hz), 5.10 (2H, s), 6.26 (1H, d, J=12 Hz), 6.44 (1H, d, J=12 Hz), 7.7–7.85 (2H, m), 7.1–7.4 (7H, m).

EXAMPLE 20

Production of 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) p-methoxybenzyl ester

p-Methoxybenzyl 7-amino-3-[2-(4-chlorothiazol-5-yl) vinyl]-3-cephem-4-carboxylate (cis-isomer) (1.205 g, 2.60 mmol) and 2-(2-tritylaminothiazol)-2-methoxyimino-acetic acid (syn-isomer) (1.153 g, 2.60 mmol) were dissolved in methylene chloride (30 ml), to which were added pyridine (0.84 ml, 10.4 mmol) and then phosphorus oxychloride (0.33 ml, 3.64 mmol) at −20° C. under cooling. The reaction solution was stirred for 20 minutes at 0° C. and poured into a mixture of ice-water (100 ml) and ethyl acetate (100 ml), followed by stirring. The mixture obtained was allowed to stand until it separated into the aqueous phase and organic phase. The organic phase was separated from the aqueous phase, washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue obtained was purified by flash-column chromatography on a column of silica-gel (Wako-gel C-300) (50 g) as developed with benzene-ethyl acetate (5:1) as eluent. The titled compound was obtained (yield 1.665 g, 72%).

NMR, δ ($CDCl_3$): 3.20 (1H, d, J=18 Hz), 3.44 (1H, d, J=18 Hz), 3.76 (3H, s), 4.03 (3H, s), 5.07 (2H, s), 5.08 (1H, d, J=5 Hz), 5.94 (1H, dd, J=5 Hz, 9 Hz), 6.33 (1H, d, J=12 Hz), 6.59 (1H, d, J=12 Hz), 6.7–7.4 (22H, m), 8.50 (1H, s).

EXAMPLE 21

Production of 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) sodium salt

p-Methoxybenzyl 7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylate syn-isomer, cis-isomer) (0.856 g, 0.962 mmol) was dissolved in anisole (2 ml), to which was added dropwise trifluoroacetic acid (8 ml) under ice-cooling. The mixture obtained was stirred for 1 hour under ice-cooling and then admixed with isopropyl ether (50 ml) to deposit a precipitate. The precipitate was removed by filtration, washed with isopropyl ether and dried under reduced pressure. The titled compound (the carboxylic acid) was obtained in the form of its trifluoroacetate (0.586 g) (as an acid-addition salt with trifluoroacetic acid). The compund obtained was mixed water (3 ml) and sodium hydrogen carbonate (0.242 g), and the resulting solution was purified by column-chromatography on a column of Diaion HP-20 as eluted with water and then with 30% aqueous acetone. The fractions of the eluate containing the desired compound were combined together and concentrated under reduced pressure, followed by lyophilization. The titled compound was obtained (yield 0.433 g, 82%).

NMR, δ (D_2O): 3.43 (1H, d, J=18 Hz), 3.70 (1H, d, J=18 Hz), 4.03 (3H, s), 5.42 (1H, d, J=5 Hz), 5.90 (1H, d, J=5 Hz), 6.48 (1H, d, J=12 Hz), 6.71 (1H, d, J=12 Hz), 7.06 (1H, s), 8.87 (1H, s).

EXAMPLE 22

Production of 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) pivaloyloxymethyl ester

7-[2-Methoxyimino-2-aminothiazol-4-yl)acetamido]-3-[2-(4-chlorothiazol-5yl-)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) sodium salt (0.104 g, 0.188 mmol) was dissolved in dimethylformamide (3 ml). Under ice-cooling, the resultant solution was admixed with a solution of iodomethyl pivalate in dimethylformamide (1 ml), and the mixture obtained was stirred for 10 minutes. To the reaction solution were added ice-water (20 ml) and ethyl acetate (20 ml). The resulting mixture was well agitated and then allowed to stand until it separated into the aqueous phase and organic phase. The organic phase was separated from the aqueous phase, washed twice with 10 ml-portions of water and with 10 ml of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue obtained was purified by flash-column chromatography on a column of silica-gel (Wako-gel C-300) (10 g) as eluted with ethyl acetate. The titled compound was afforded (yield 0.940 g, 78%).

NMR, δ ($CDCl_3$): 1.13 (9H, s), 3.30 (1H, d, J=18 Hz), 3.51 (1H, d, J=18 Hz), 5.17 (1H, d, J=5 Hz), 5.43 (2H, broad s), 5.75 (1H, d, J=6 Hz), 5.80 (1H, d, J=6 Hz), 6.06 (1H, dd, J=5 Hz), 6.40 (1H, d, J=12 Hz), 6.66 (1H, d, J=12 Hz), 6.78 (1H, s), 7.65 (1H, d, J=9 Hz), 8.54 (1H, s).

EXAMPLE 23–28

The following compounds were produced in the same manner as in Example 20 described above.

Example 23

7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl) acetamido]-3-[2-(thiazol-2-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer) diphenylmethyl ester (Yield 72%).

NMR, δ ($CDCl_3$): 3.45 (1H, d, J=18 Hz), 3.67 (1H, d, J=18 Hz), 4.04 (3H, s), 5.16 (1H, d, J=5 Hz), 5.97 (1H, dd, J=5 Hz, 9 Hz), 6.58 (1H, s), 6.73 (1H, s), 6.85 (1H, s), 6.9–7.5 (29H, m), 7.74 (1H, d, J=3 Hz).

EXAMPLE 24

7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl) acetamino]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer) diphenylmethyl ester (Yield 68%).

NMR, δ ($CDCl_3$): 2.63 (3H, s), 3.56 (2H, broad s), 4.04 (3H, s), 5.06 (1H, d, J=5 Hz), 5.88 (1H, dd, J=5 Hz, 9 Hz), 6.73 (1H, s), 6.82 (1H, d, J=16 Hz), 6.98 (1H, s), 7.0–7.5 (H29, m). EXAMPLE 25

7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl) acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxilyc acid (syn-isomer, cis-isomer) diphenylmethyl ester (Yield 76%).

NMR, δ ($CDCl_3$): 2.60 (3H, s), 3.27 (1H, d, J=18 Hz), 3.48 (1H, D, J=18 Hz), 4.04 (3H, s), 5.16 (1H, d, J=5 Hz), 5.97 (1H, dd, J=5 Hz, 9 Hz), 6.13 (1H, d, J=12 Hz), 6.41 (1H, d, J=12 Hz), 6.71 (1H, s), 6.85 (1H, s), 6.9–7.5 (28H, m).

EXAMPLE 26

7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl) acetamidol]-3-[2-(thiazol-4-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) p-methoxybenzyl ester (Yield 75%).

NMR, δ ($CDCl_3$): 3.40 (1H, d, J=18 Hz), 3.62 (1H, d, J=18 Hz), 3.77 (3H, s), 4.04 (3H, s), 5.10 (1H, d, J=5 Hz), 5.11 (2H, s), 5.89 (1H, dd, J=5 Hz), 9 Hz), 6.53 (2H, s), 6.7–7.5 (23H, m), 8.66 (1H, d, J=2Hz).

EXAMPLE 27

7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl) acetamido]-3-[2-(thiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) diphenylmethyl ester (Yield 69%).

NMR, δ ($CDCl_3$): 3.27 (1H, d, J=18 Hz), 3.46 (1H, d, J=18 Hz), 4.04 (1H, d, J=5 Hz), 5.96 (1H, dd, J=5 Hz, 9 Hz), 6.23 (1H, d, J=12 Hz), 6.50 (1H, d, J=12 Hz), 6.71 (1H, s), 6.83 (1H, s), 6.9–7.5 (27H, m), 7.61 (1H, s), 8.57 (1H, s).

EXAMPLE 28

7-[2-methoxyimino-2-(2-tritylaminothiazol-4-yl) acetamido]-3-[2-(2,4-dichlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) p-methoxybenzyl ester (Yield 81%).

NMR, δ ($CDCl_3$): 3.21 (1H, d, J=18Hz), 3.42 (1H, d, J=18 Hz), 3.76 (3H, s), 4.04 (3H, s), 5.09 (1H, d, J=5 Hz), 5.11 (2H, s), 5.95 (1H, dd, J=5 Hz, 9 Hz), 6.25 (1H, d, J=12 Hz), 6.47 (1H, d, J=12 Hz), 6.7–7.4 (22H, m).

EXAMPLE 29–34

The following compounds in the form of sodium salt or trifluoroacetate were produced in the same manner as in the foregoing Example 21.

EXAMPLE 29

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-2-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer) sodium salt (Yield 82%).

NMR, δ (D_2O): 3.82 (2H, broad s), 4.02 (3H, s), 5.32 (1H, d, J=5 Hz), 5.85 (1H, d, J=5 Hz), 6.99 (1H, d, J=16 Hz), 7.03 (1H, s), 7.46 (1H, d, J=16 Hz), 7.49 (1H, d, J=3 Hz), 7.76 (1H, d, J=3 Hz).

EXAMPLE 30

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazo-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer) trifluoroacetate (Yield 88%).

NMR, δ (CD_3SOCD_3): 2.62 (3H, s), 3.75 (2H, broad s), 3.83 (3H, s), 5.18 (1H, d, J=5 Hz), 5.75 (1H, dd, J=5 Hz, 9 Hz), 6.75 (1H, s), 7.13 (2H, s), 7.60 (1H, s), 9.58 (1H, d, J=9 Hz).

EXAMPLE 31

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) trifluoroacetate (Yield 78%).

NMR, δ (CD_3SOCD_3): 2.59 (3H, s), 3.41 (1H, d, J=18 Hz), 3.53 (1H, d, J=18 Hz), 3.84 (3H, s), 5.28 (1H, d, J=5 Hz), 5.82 (1H, dd, J=5 Hz, J=9 Hz), 6.22 (1H, d, J=12 Hz), 6.63 (1H, d, J=12 Hz), 6.73 (1H, s), 7.57 (1H, s), 9.60 (1H, d, J=9 Hz).

EXAMPLE 32

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-4-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) sodium salt (Yield 74%).

NMR, δ (D_2O): 3.45 (1H, d, J=18 Hz), 3.58 (1H, d, J=18 Hz), 4.03 (3H, s), 5.33 (1H, d, J=5 Hz), 5.84 (1H, d, J=5 Hz), 6.56 (1H, d, J=12 Hz), 6.71 (1H, d, J=12 Hz), 7.06 (1H, s), 7.51 (1H, d, J=2 Hz), 8.99 (1H, d, J=2 Hz).

EXAMPLE 33

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) sodium salt (Yield 78%).

NMR, δ (D_2O): 3.48 (1H, d, J=18 Hz), 3.70 (1H, d, J=18 Hz), 4.05 (1H, s), 5.45 (1H, d, 2J=5 Hz), 5.90 (1H, d, J=5 Hz), 6.39 (1H, d, J=12 Hz), 6.81 (1H, d, J=12 Hz), 7.08 (1H, s), 7.86 (1H, s), 8.90 (1H, s).

EXAMPLE 34

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2,4-dichlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) sodium salt (Yield 78%).

NMR, δ (D_2O): 3.46 (1H, d, J=18 Hz), 3.67 (1H, d, J=18 Hz), 4.04 (3H, s), 5.43 (1H, d, J=5 Hz), 5.91 (1H,

d, J=5 Hz), 6.45 (1H, d, J=12 Hz), 6.64 (1H, d, J=12 Hz), 7.08 (1H, s).

EXAMPLES 35–39

The following compounds were produced in the same manner as in Example 22 described hereinbefore.

EXAMPLE 35

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer) (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester (Yield 62%).

NMR, δ ($CDCl_3$): 2.21 (3H, s), 2.69 (3H, s), 3.65 (1H, d, J=18 Hz), 3.75 (1H, d, J=18 Hz), 4.04 (3H, s), 4.93 (1H, d, J=16 Hz), 5.12 (1H, J=5 Hz), 5.14 (1H, d, J=16 Hz), 5.14 (2H, broad), 5.99 (1H, dd, J=5 Hz, J=9 Hz), 6.81 (1H, s), 6.92 (1H, d, J=16 Hz), 7.24 (1H, d, J=16 Hz), 7.53 (1H, s), 7.64 (1H, d, J=9 Hz).

EXAMPLE 36

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester (Yield 69%).

NMR, δ ($CDCl_3$): 2.08 (3H, s), 2.64 (3H, s), 3.45 (1H, d, J=18 Hz), 3.54 (1H, d, J=18 Hz), 4.04 (3H, s), 4.80 (1H, d, J=16 Hz), 4.99 (1H, d, J=16 Hz), 5.22 (1H, d, J=5 Hz), 5.4 (2H, broad), 6.10 (dd, J=5 Hz, 9 Hz), 6.17 (1H, d, J=12 Hz), 6.60 (1H, d, J=12 Hz), 6.78 (1H, s), 7.46 (1H, s), 7.72 (1H, d, J=9 Hz).

EXAMPLE 37

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-4-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) pivaloyloxymethyl ester (Yield 72%).

NMR, δ ($CDCl_3$): 1.16 (9H, s), 3.48 (1H, d, J=18 Hz), 3.68 (1H, d, J=18 Hz), 4.04 (3H, s), 5.16 (1H, d, J=5 Hz), 5.75 (1H, d, J=6 Hz), 5.86 (1H, d, J=6 Hz), 5.94 (1H, dd, J=5 Hz, 9 Hz), 6.51 (1H, d, J=12 Hz), 6.58 (1H, d, J=12 Hz), 6.88 (1H, s), 7.19 (1H, d, J=2 Hz), 8.66 (1H, d, J=2 Hz).

EXAMPLE 38

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) pivaloyloxymethyl ester (Yield 76%).

NMR, δ ($CDCl_3$): 1.13 (9H, s), 3.32 (1H, d, J=18 Hz), 3.50 (1H, d, J=18 Hz), 4.04 (3H, s), 5.19 (1H, d, J=5 Hz), 5.74 (1H, d, J=6 Hz), 5.81 (1H, d, J=6 Hz), 6.02 (1H, dd, J=5 Hz, 9 Hz), 6.35 (1H, d, J=12 Hz), 6.68 (1H, d, J=12 Hz), 6.88 (1H, s), 7.41 (1H, d, J=9 Hz), 7.75 (1H, s), 8.66 (1H, s).

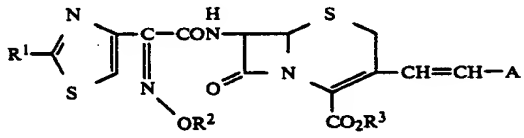
EXAMPLE 39

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2,4-dichlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) pivaloyloxymethyl ester (Yield 71%).

NMR, δ ($CDCl_3$): 1.16 (9H, s), 3.30 (1H, d, J=18 Hz), 3.52 (1H, d, J=18 Hz), 4.05 (3H, s), 5.16 (1H, d, J=6 Hz), 5.78 (1H, d, J=6 Hz), 5.81 (1H, d, J=6 Hz), 6.05 (1H, dd, J=5 Hz, 9 Hz), 6.38 (1H, d, J=12 Hz), 6.58 (1H, d, J=12 Hz), 6.91 (1H, s).

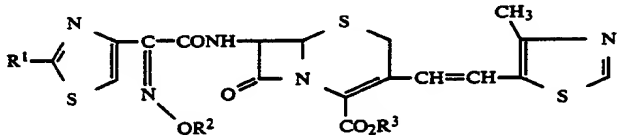
What we claim is:

1. A cephalosporin compound of the formula (I)



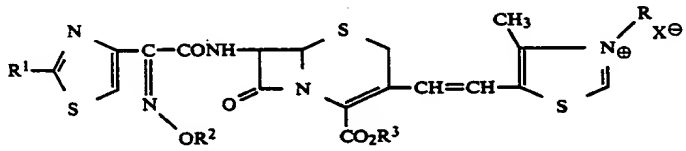
wherein R^1 is an amino group or a protected amino group; R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group; R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group; A is thiazolyl group, a lower-alkyl-thiazolyl group, a halo-thiazolyl group, or a 3-lower-alkylthiazolio group optionally substituted with one lower alkyl group, with an iodide or tirfluoroacetate counterion, and a pharmaceutically acceptable salt or ester of said cephalosporin compound.

2. A cephalosporin compound as claimed in claim 1 which if of the formula (Ic)



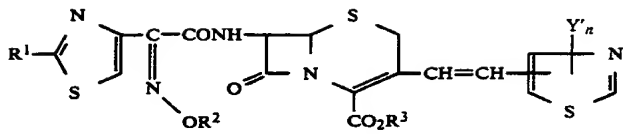
wherein R^1 is an amino group or a protected amino group, R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, and R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group.

3. A cephalosporin compound as claimed in claim 1 which is of the formula (Id)



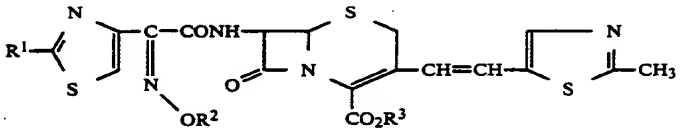
wherein R^1 is an amino group or a protected amino group, R^2 is a lower (C_1–C_6) alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, R is a lower alkyl group and X is an iodide ion or a trifluoroacetate ion.

4. A cephalosporin compound as claimed in claim 1 which is of the formula (Ie)


(Ie)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower (C_1–C_3) alkyl group, a carboxymethyl group, or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, and Y' is a hydrogen atom or a halogen atom, and n is a whole number of 1 or 2.

5. A cephalosporin compound as claimed in claim 1 which is of the formula (If)


(If)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower (C_1–C_6) alkyl group, a caroboxymethyl group or a protected carboxymethyl group, and R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group.

6. A compound as claimed in claims 1, 2, 3, 4 or 5 in which R^1 is an amino group, R^2 is a methyl group or a carboxymethyl group, and R^3 is sodium atom, benzhydryl group, p-methoxybenzyl group, diphenylmethyl group, pivaloyloxymethyl group or (5-methyl-2-oxo-1,3-dioxolene-4-yl)-methyl group.

7. A compound as claimed in claim 1 which is selected from the group consisting of

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-2-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer);

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-4-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) and its sodium salt and its pivaloyloxymethyl ester; and

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer), it sodium salt, and its pivaloyloxymethyl ester.

8. A compound as claimed in claim 1 which is selected from the group of consisting of

7-[2-carboxymethoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) and its acid addition salt with trifluoroacetic acid,

7-[2-t-butoxycarbonylmethoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer); and

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer), its sodium salt, its acid addition salt with trifluoroacetic acid, and its (5-methyl-2-oxo-1,3-dioxolene-4-yl)-methyl ester.

9. A compound as claimed in claim 1 which is selected from the group consisting of

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer), its sodium salt and its pivaloyloxymethyl ester; and

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2,4-dichlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer), it sodium salt and its pivaloyloxymethyl ester.

10. A compound as claimed in claim 1 which is 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(3,4-dimethyl-5-thiazolio)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) iodide or its acid addition salt with trifluoroacetic acid.

11. 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) sodium salt.

12. 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) pivaloyloxymethyl ester.

13. A compound which is selected from the group consisting of 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer), a sodium salt thereof, a pivaloyloxymethyl ester thereof, a (5-methyl-2-oxo-1,3-dioxolene-4-yl)-methyl ester thereof and an acid addition salt thereof with trifluoroacetic acid.

14. A pharmaceutical, antibacterial composition which comprises an antibacterially effective amount of the compound of the formula (I) as defined in claim 1 or the compound of the formula (Ic) to (If) as defined in anyone of claims 2 to 5 or a pharmaceutically acceptable salt or ester thereof, as the active ingredient, in combination with a pharmaceutically acceptable carrier for the active ingredient.

* * * * *

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

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1	4,839,350	185	2910	----	07/036,124	06/13/89	04/07/87	12	NO	PAID

ITM NBR	ATTY DKT NUMBER
1	XI

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
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3

Chronology for IND 53, 866 (Cefditoren Pivoxil)		
Date	**To/From**	**Subject**
5/21/1997	FDA/TAP	Formal request for pre-IND meeting
6/3/1997	FDA/TAP	Briefing document for Pre-IND meeting to be held 6/18/1997
6/18/1997		Pre-IND meeting held at FDA to discuss the clinical development plan for cefditoren
6/30/1997	FDA/TAP	Revised list of comparators for TAP's clinical trials for pharyngitis, sinusitis, bronchitis, pneumonia, and skin indications
7/13/1997	FDA/TAP	Fax inquiring about the presentation of foreign reports done under GLP management and requesting a teleconference to discuss TAP's selection of comparators
7/21/1997	TAP/FDA	Fax containing FDA response to TAP comparator selection for cefditoren clinical trials
7/31/1997	FDA/TAP	Original submission of IND
8/6/1997	FDA/TAP	Formal letter acknowledging receipt of the cefditoren pivoxil IND
8/14/1997	FDA/TAP	E-mail request from medical reviewer for protocols included in the original IND to be submitted on diskette in Word Perfect 6.1 format
8/18/1997	FDA/TAP	(IND Amendment 001) Response to FDA Request for Information regarding location of certain items in CMC section and clarification of organizational structure
8/26/1997	FDA/TAP	Telephone call from FDA stating that the 30 day safety review of the initial IND submission will be complete on 9/1/1997 and that clinical trials may begin
8/26/1997	FDA/TAP	(IND Amendment 002) Copies of protocols CEF-97-002 and CEF-97-003 in Word Perfect 6.1 Format
8/26/1997	FDA./TAP	Telephone call from FDA requesting supplemental information on the crystalline cefditoren manufacturing method and the crystalline-to-amorphous manufacturing method
8/27/1997	FDA/TAP	(IND Amendment 003) Response to FDA Request for Information: Supplemental details on final drug product manufacturing
8/26/1997	TAP/FDA	Request via e-mail for three additional copies of volume 2 and two additional copies of volume 8 from original IND
8/28/1997	FDA/TAP	Provided additional desk copies of certain volumes of the original IND submission in response to FDA request
9/19/1997	TAP/FDA	Formal letter recognizing completion of IND review and request for more data and information
9/30/1997	TAP/FDA	Copy of FDA meeting minutes from pre-IND meeting on 6/18/1997
10/16/1997	FDA/TAP	(IND Amendment 004) Responses to FDA Requests for Information from 9/19/1997 letter; Response from FDA Requested
10/24/1997	FDA/TAP	(IND Amendment 005) Amendment to Amendment 004's cover letter
10/24/1997	TAP/FDA	Formal letter containing CMC requests that should be addressed as the information becomes available

Date	To/From	Subject
10/29/1997	FDA/TAP	(IND Amendment 006) New Investigators, Amended CRO Responsibilities, CMC Information, Packaging, and Labeling for CEF-97-003
11/17/1997	FDA/TAP	(IND Amendment 007) Amendment #1 to protocol CEF-97-003
11/19/1997	FDA/TAP	(IND Amendment 008) CEF-97-008 (New Protocol): Information including Investigator and CMC Information
12/1/1997	TAP/FDA	Fax containing statistical comments for protocols CEF-97-003 and CEF-97-008
12/1/1997	FDA/TAP	(IND Amendment 009) New investigators for CEF-97-003
12/10/1997	TAP/FDA	Formal letter containing statistical comments regarding protocols CEF-97-003 and CEF-97-008
12/11/1997	FDA/TAP	(IND Amendment 010) CEF-97-007 including Administrative Change #1 (New Protocol): Information including investigator and CMC Information
12/12/1997	FDA/TAP	(IND Amendment 011) Response to FDA Request for Information in letter from Agency dated 10/24/1997: Detailed, stepwise method of drug substance synthesis
12/22/1997	FDA/TAP	(IND Amendment 012) CEF-97-012: Protocol amendment, new investigator and CMC Information
1/5/1998	FDA/TAP	(IND Amendment 013) New and/or revised investigator information for multiple protocols; Administrative Change #1 to CEF-97-010
1/16/1998	TAP/FDA	Telephone call informing the Agency of TAP's intent to pursue a pediatric indication and response from Dr. Chikami regarding superiority claims for cefditoren
1/16/1998	FDA/TAP	(IND Amendment 014) Response to FDA Letter dated 12/10/1997 regarding statistical comments on clinical protocols
1/16/1998	FDA/TAP	Fax containing a list of amendments made to the IND through Amendment 014
1/20/1998	TAP/FDA	E-mail requesting TAP to describe and clarify what the company means by dose control studies
1/21/1998	FDA/TAP	(IND Amendment 015) Amendment #1 to CEF-97-002
1/23/1998	TAP/FDA	Biopharm comments regarding IND Amendment 004
1/28/1998	FDA/TAP	(IND Amendment 016) Pharmacology and bioavailability information amendment
1/30/1998	FDA/TAP	(IND Amendment 017) New and/or Revised Investigator Information for CEF-97-003, CEF-97-007, and CEF-97-008
2/3/1999	FDA/TAP	Telephone call inquiring if the Agency would accept English summaries or just entire English translations of Japanese references
2/10/1998	FDA/TAP	(IND Amendment 018) Information on Lilly del Caribe Manufacturing; Transfer of Manufacturing Process from Meiji Seika Kaisha, Ltd. To Lilly del Caribe; CEF-97-013 (New Protocol): Investigator and CMC Information
2/18/1998	FDA/TAP	(IND Amendment 019) Amendment #1 to CEF-97-008 and CEF-97-013
2/19/1998	FDA/TAP	(IND Amendment 020) Microbiology Information Amendment

Date	To/From	Subject
3/5/1998	FDA/TAP	(IND Amendment 021) CEF-97-004 (New Protocol): Protocol, Investigator, and CMC Information; New and/or Revised Investigators for CEF-97-002, CEF-97-003, CEF-97-007, and CEF-97-008
3/9/1998	FDA/TAP	(IND Amendment 022) CEF-97-006 (New Protocol): Protocol, Investigator, and CMC Information
3/12/1998	FDA/TAP	(IND Amendment 023) CEF-97-005 (New Protocol incorporating Amendment 1): Protocol, Investigator, and CMC Information
3/17/1998	FDA/TAP	(IND Amendment 024) CEF-97-010 (New Protocol): Protocol, Investigator, and CMC Information
3/24/1998	TAP/FDA	Fax containing statistical comments regarding CEF-97-010
3/25/1998	FDA/TAP	Fax containing response to FDA Fax dated 3/24/97 regarding statistical comments for CEF-97-010
3/27/1998	FDA/TAP	(IND Amendment 025) Response to FDA Letter dated January 23, 1998 concerning biopharmaceutical and clinical items
3/30/1998	FDA/TAP	(IND Amendment 026) Amendment #2 to CEF-97-002; New and/or Revised Investigators for Multiple Protocols
4/3/1998	FDA/TAP	(IND Amendment 027) Stability Data for PVK Tablets used in CEF-97-010 and CEF-97-008 protocols
4/6/1998	FDA/TAP	(IND Amendment 028) Response to FDA Request for Information on statistics used and sample size calculations for certain protocols
4/8/1998	TAP/FDA	Telephone call infoming TAP of two possible incorrect toxicology tables in the original IND
4/20/1998	FDA/TAP	(IND Amendment 029) Correction to 2 toxicology tables submitted in original IND
4/22/1998	TAP/FDA	Letter notifying Office of International Affiars of TAP's plans to ship cefditoren pivoxil tablets and Vantin to South Africa for Phase III clinical study
4/22/1998	TAP/FDA	Telephone call to discuss whether pediatriac and adult cefditoren NDAs could be combined into one large submission
5/1/1998	FDA/TAP	(IND Amendment 030) New and/or Revised Investigator Information for Multiple Protocols; Amendment #2 to CEF-97-003; Amendment #1 to CEF-97-004; Administrative Change #1 to CEF-97-008; Administrative Change #1 to CEF-97-010
5/15/1998	FDA/TAP	(IND Amendment 031) Pharmacology, Toxicology, and Clinical Reports (39 total)
5/18/1998	FDA/TAP	(IND Amendment 032) Method validation information to support Report No. 744-10
5/22/1998	FDA/TAP	(IND Amendment 033) CEF-97-016 (New Protocol): Protocol, Investigator, and CMC Information
6/2/1998	FDA/TAP	(IND Amendment 034) New and/or Revised Investigators for Multiple Protocols; Amendment #1 to CEF-97-007
6/3/1998	FDA/TAP	(IND Amendment 035) CEF-97-015 (New Protocol): Protocol, Investigator, and CMC Information; Amendment #3 to CEF-97-002
6/4/1998	FDA/TAP	(IND Amendment 036) Response to FDA Request for Information (from letter dated October 24, 1997); 10 Chemistry reports for bulk cefditoren

Date	To/From	Subject
6/9/1998	FDA/TAP	Letter providing authorization for FDA to make reference to information contained in IND for pediatric IND
6/12/1998	FDA/TAP	(IND Amendment 037) CEF-97-009 (New Protocol): Protocol, Investigator, and CMC Information
6/12/1998	TAP/FDA	Telephone Call stating that Duricef is acceptable as a comparator for CEF-97-011
6/29/1998	FDA/TAP	(IND Amendment 038) CEF-97-011 (New Protocol): Protocol, Investigator, and CMC Information
6/30/1998	FDA/TAP	(IND Amendment 039) CEF-97-014 (New Protocol Incorporating Amendment #1): Protocol, Investigator, and CMC Information
7/1/1998	FDA/TAP	(IND Amendment 040) New and/or Revised Investigators for Multiple Protocols; Amendment #1 to CEF-97-009
7/14/1998	FDA/TAP	(IND Amendment 041) Amendment #1 to CEF-97-011
7/30/1998	FDA/TAP	(IND Amendment 042) Chemistry Information Amendment
7/31/1998	FDA/TAP	(IND Amendment 043) New and/or Revised Investigators for Multiple Protocols
8/11/1998	FDA/TAP	(IND Amendment 044) Formal request for CMC Meeting
8/11/1998	FDA/TAP	Telephone call for 7 day telephone report of serious adverse event
8/13/1998	FDA/TAP	(IND Amendment 045) 15 Day Adverse Drug Experience Alert Report
8/19/1998	TAP/FDA	Telephone call informing TAP that CMC meeting requested with Agency will take place on September 16, 1998
8/21/1998	FDA/TAP	(IND Amendment 046) Pharmacology Information Amendment; Corrected Version of Reference Article
8/28/1998	FDA/TAP	(IND Amendment 047) Increase Paddle Speed in Dissolution Testing
8/31/1998	FDA/TAP	(IND Amendment 048) Briefing Document for September 16, 1998 CMC Meeting
9/1/1998	FDA/TAP	(IND Amendment 049) Initial Written Adverse Reaction Report
9/2/1998	FDA/TAP	(IND Amendment 050) New and/or Revised Investigators for Multiple Protocols
9/2/1998	FDA/TAP	Fax requesting comments on submission of foreign information for cefditoren pivoxil tablet NDA
9/3/1998	TAP/FDA	Telephone call from Agency stating their comments regarding the fax of September 2, 1998
9/8/1998	FDA/TAP	(IND Amendment 051) CEF-97-017 (New Protocol): Protocol, Investigator, and CMC Information
9/16/1998		CMC Meeting held at FDA to discuss manufacturing issues
9/22/1998	FDA/TAP	(IND Amendment 052) 1998 Annual Report
10/1/1998	FDA/TAP	(IND Amendment 053) New and/or Revised Investigators for Multiple Protocols
10/8/1998	FDA/TAP	(IND Amendment 054) Amendment #1 to CEF-97-017
10/14/1998	FDA/TAP	(IND Amendment 055) CMC Meeting minutes and overheads from 9/16/98 (TAP's Version); Request for FDA's meeting minutes
10/14/1998	FDA/TAP	Telephone call for 7 day telephone report of serious adverse event

Date	To/From	Subject
10/15/1998	TAP/FDA	Telephone call requesting clarification and more information about 7 day IND Safety Report of October 14, 1998
10/20/1998	FDA/TAP	(IND Amendment 056) Initial Written Adverse Reaction Report (PE #680)
10/21/1998	FDA/TAP	(IND Amendment 057) Pharmacology/Toxicology Information Amendment
10/30/1998	TAP/FDA	Fax of FDA minutes from CMC meeting held September 16, 1998
11/2/1998	FDA/TAP	(IND Amendment 058) New and/or Revised Investigators for Multiple Protocols
11/16/1998	FDA/TAP	(IND Amendment 059) Toxicology Amendment: New related substances qualification
11/20/1998	FDA/TAP	(IND Amendment 060) Initial Written Adverse Reaction Report (PE #735)
11/23/1998	FDA/TAP	(IND Amendment 061) Response to Agency's fax on 8/18/98
11/24/1998	FDA/TAP	(IND Amendment 062) CEF-98-023 (New Protocol): Protocol, Investigator, and CMC Information
12/1/1998	TAP/FDA	Fax containing list of US centers that conduct blister fluid studies (responding to voicemail request from TAP made on November 20, 1998)
12/1/1998	FDA/TAP	(IND Amendment 063) New and/or Revised Investigators for Multiple Protocols
12/8/1998	FDA/TAP	(IND Amendment 064) Request for Response by FDA regarding revision of clinical response definitions
12/11/1998	FDA/TAP	(IND Amendment 065) Response to FDA Request for Information from 9/16/98 CMC meeting
12/14/1998	FDA/TAP	(IND Amendment 066) Request for Response by FDA regarding CANDA and Section 11 waiver for NDA
12/15/1998	TAP/FDA	Telephone call stating that the Agency will be available for a teleconference regarding carnitine on January 20, 1999
12/15/1998	TAP/FDA	Fax requesting documents in preparation for carnitine teleconference
12/28/1998	FDA/TAP	(IND Amendment 067) New and/or Revised Investigators for Multiple Protocols
12/29/1998	FDA/TAP	(IND Amendment 068) Response to FDA request from 9/16/98 CMC meeting: Entire product catalog from Nippon Chemical
1/7/1999	FDA/TAP	E-mail to Project Manager regarding carnitine teleconference attendees, reminder of request for FDA comments on ACTA as a starting material, and reminder of request for FDA comments on clinical definitions
1/8/1999	FDA/TAP	Response to FDA fax dated 12/15/98 consisting of further information regarding carnitine and consultant CVs
1/21/1999	TAP/FDA	E-mail from Project Manager stating Dr. Shetty's response to TAP's submission on 12/11/98 regarding ACTA as starting material
1/22/1999	FDA/TAP	E-mail to Project Manager requesting clarification of the FDA response to ACTA as a starting material dated 1/21/99
1/25/1999	FDA/TAP	(IND Amendment 069) Follow Up #1 to a Written Adverse Reaction Report
1/27/1999	FDA/TAP	(IND Amendment 070) Amendment #2 to Protocol CEF-97-004

Date	To/From	Subject
1/29/1999	FDA/TAP	(IND Amendment 071) Response to FDA Request: Justification of dissolution method
1/29/1999	FDA/TAP	Telephone call to Project Manager requesting FDA comments on clinical definitions (received a response) and clarification on submitting foreign references to the upcoming NDA
2/2/1999	FDA/TAP	(IND Amendment 072) New and/or Revised Investigators for Multiple Protocols
2/9/1999	TAP/FDA	E-mail from Project Manager stating she will be on maternity leave and naming the interim project manager
2/19/1999	FDA/TAP	(IND Amendment 073) Response to Info Request and Request for FDA Response regarding ACTA as starting material
2/24/1999	FDA/TAP	Fax and e-mail requesting Dr. Ross to review and comment on the modification of clinical definitions in cefditoren pivoxil studies
3/1/1999	FDA/TAP	(IND Amendment 074) New and/or Revised Investigators for Multiple Protocols
3/4/1999	FDA/TAP	(IND Amendment 075) CEF-97-018 (New Protocol): Protocol, Investigator, and CMC Information
3/23/1999	TAP/FDA	Telephone call from Dr. Shetty regarding ACTA as a starting material and questions about GCLE
4/1/1999	FDA/TAP	(IND Amendment 076) New and/or Revised Investigators for Multiple Protocols
5/3/1999	FDA/TAP	(IND Amendment 077) Amendment #2 to CEF-97-007; Amendments #2 and #3 to CEF-97-014;New and/or Revised Investigators for Multiple Protocols
5/26/1999	FDA/TAP	(IND Amendment 078) New and/or Revised Investigators for Multiple Protocols
6/3/1999	TAP/FDA	Telephone call from Dr. Kenneth Seethaler concerning toxicology reports
6/7/1999	FDA/TAP	(IND Amendment 079) Request for tradename review
6/14/1999	FDA/TAP	Telephone call to Project Manager to discuss the Pre-NDA meetings , outstanding requests to the Agency, IND Annual Report Waiver, and english translations of batch records
6/15/1999	FDA/.TAP	Return of Dr. Seethaler's telephone call from 6/3/99 regarding specification for related substance P3 in toxicology report 823/18
6/17/1999	FDA/TAP	(IND Amendment 080) Request for Pre-NDA meetings
6/17/1999	FDA/TAP	(IND Amendment 081) CEF-98-030 (New Protocol): Protocol, Investigator, and CMC Information
6/28/1999	FDA/TAP	Telephone call to Project Manager regarding Pre-NDA CMC and clinical/CANDA meetings and requesting updates on carnitine, tradename review, & clinical definitions
7/12/1999	FDA/TAP	(IND Amendment 082) New and/or Revised Investigators for Multiple Protocols
7/13/1999	FDA/TAP	(IND Amendment 083) Briefing Document for 8/4/99/98 Pre-NDA CMC Meeting
7/14/1999	TAP/FDA	Telephone call from Project Manager regarding tradename review status

Date	To/From	Subject
7/19/1999	FDA/TAP	Telephone call to Project Manager to follow-up on annual report waiver, CMC Pre-NDA Meeting, and modification of clinical definitions
7/19/1999	FDA/TAP	(IND Amendment 084) Response to FDA Request: Info. relating to GCLE to Access ACTA as starting material
7/26/1999	FDA/TAP	Fax to Project Manager consisting of revised Points of Discussion (from Briefing Document of 7/13/99) for Pre-NDA meeting
7/27/1999	FDA/TAP	(IND Amendment 085) Toxicology, Pharmacology, and Metabolism Reports
7/30/1999	FDA/TAP	(IND Amendment 086) New and/or Revised Investigators for Multiple Protocols
8/2/1999	FDA/TAP	(IND Amendment 087) CEF-99-032 (New Protocol): Protocol, Investigator, and CMC Information
8/3/1999	FDA/TAP	(IND Amendment 088) Briefing Document for Pre-NDA Meeting (Preclinical, Micro., and Clincal) on 8/26/99
8/4/1999		CMC Pre-NDA Meeting
8/9/1999	TAP/FDA	Fax from Project Manager stating FDA attendees for Pre-NDA Meeting (CMC) and Pre-NDA Meeting (Clinical)
8/10/1999	FDA/TAP	Telephone call to Project Manager regarding clarification on FDA's comments at pre-NDA meeting about additional dissolution data to justify method change
8/12/1999	TAP/FDA	Telephone call from Project Manager stating the biopharm reviewer requesting a more complete dissolution profile for FDA acceptance of paddle speed change
8/12/1999	TAP/FDA	Telephone call to Product Manager and Medical Reviewer requesting documents for Clinical Pre-NDA Meeting (Japanese PI, TAP's draft PI, further information on the CAP studies, post-marketing surveillance from Meiji & contents of briefing document on diskette)
8/13/1999	TAP/FDA	Telephone call from Medical Reviewer requesting electronic copies of protocols in preparation for Clinical Pre-NDA Meeting
8/13/1999	FDA/TAP	(IND Amendment 089) Response to FDA Request: Four clinical protocols on diskette
8/17/1999	FDA/TAP	(IND Amendment 090) Response to FDA Request: Meiji Seika Kaisha's Post Marketing Surveillance Report
8/17/1999	FDA/TAP	(Desk Copy) FDA Request for Clinical Pre-NDA briefing document on diskette and the MEIACT PSUR
8/23/1999	FDA/TAP	Telephone call to Proejct Manager to discuss the contents of the Clinical Pre-NDA Meeting
8/25/1999	TAP/FDA	Fax from Project Manager containing minutes from 8/4/99 CMC Pre-NDA Meeting
8/26/1999		Clinical Pre-NDA Meeting
8/31/1999	FDA/TAP	(IND Amendment 091) New and/or Revised Investigators for Multiple Protocols
9/7/1999	FDA/TAP	(IND Amendment 092) CMC Pre-NDA Meeting Minutes from 8/4/99 (TAP's version)
9/10/1999	FDA/TAP	(IND Amendment 093) Clinical Information Amendment: Drug Metabolism Report No. 2 (for Study CEF-97-012)

Date	To/From	Subject
9/28/1999	FDA/TAP	(IND Amendment 094) Drug Metabolism, Pharmacokinetic, Analytical Method, and Microbiology Reports
9/30/1999	FDA/TAP	(IND Amendment 095) Annual Report for reporting period 8/1/98 - 7/31/99
10/1/1999	FDA/TAP	(IND Amendment 096) Revised Investigators for Multiple Protocols
10/6/1999	FDA/TAP	Telephone call to Project Manager to follow-up on some outstanding questions regarding the NDA and to discuss TAP's strategy for the CAP indication
10/25/1999	FDA/TAP	Telephone call to Project Manager regarding the filing of issued and draft patents
10/26/1999	TAP/FDA	Fax from Project Manager containing minutes from 8/26/99 Clinical Pre-NDA Meeting
10/26/1999	TAP/FDA	Formal letter stating that the proposed name Spectracef is acceptable
10/28/1999	FDA/TAP	(IND Amendment 097) Revised Investigators for Multiple Protocols
11/3/1999	FDA/TAP	Telephone call to Susan Lang regarding the LOD increase in the foil/foil blister packaging
11/10/1999	FDA/TAP	Telephone call to Susan Lang regarding the reporting of stability data for container/closure systems not intended for marketing
11/18/1999	FDA/TAP	(IND Amendment 098) Revised LOS Specification
12/1/1999	FDA/TAP	(IND Amendment 099) New and/or Revised Investigators for Multiple Protocols
12/6/1999	FDA/TAP	Telephone call to Project Manager informing the Division of the intent to omit the results for 3 investigators from the safety and efficacy analyses in the NDA
12/10/1999	FDA/TAP	(IND Amendment 100) Follow-Up from CMC Pre-NDA Meeting: Dissolution Justification Report
12/14/1999	TAP/FDA	Telephone call from Project Manager clarifying the proper location for the deferral from pediatric studies in the NDA
12/20/1999	FDA/TAP	(IND Amendment 101) Discrepancy between TAP's and FDA's Clinical Pre-NDA meeting minutes
1/4/2000	FDA/TAP	(IND Amendment 102) Protocol Amendment: Study CEF-97-002 Amd. No. 4; Study CEF-97-006 Amd. No. 1; Investigators
1/28/2000	FDA/TAP	(IND Amendment 103) New and/or Revised Investigators for Mulitple Protocols
3/30/2000	FDA/TAP	(IND Amendment 104) New and/or Revised Investigators for Mulitple Protocols
4/13/2000	FDA/TAP	(IND Amendment 105) IND Safety Report - Initial Written Report
5/1/2000	FDA/TAP	(IND Amendment 106) Sponsor Name Change
5/1/2000	FDA/TAP	(IND Amendment 107) IND Safety Report - Follow-up Report #1
5/5/2000	FDA/TAP	(IND Amendment 108) New and/or Revised Investigators for Mulitple Protocols
6/1/2000	FDA/TAP	(IND Amendment 109) New and/or Revised Investigators for Mulitple Protocols
6/13/2000	FDA/TAP	(IND Amendment 110) IND Safety Report - Initial Written Report and Follow-up Report #1
6/19/2000	FDA/TAP	(IND Amendment 111) IND Safety Report - Initial Written Report

Date	To/From	Subject
7/11/2000	FDA/TAP	(IND Amendment 112) New and/or Revised Investigators for Mulitple Protocols
7/12/2000	FDA/TAP	(IND Amendment 113) IND Safety Report - Follow-up #2
8/1/2000	FDA/TAP	(IND Amendment 114) Request for Study Design Review: Study CEF-00-034 Cefditoren vs. Levaquin
8/4/2000	FDA/TAP	(IND Amendment 115) Protocol Amendment: Change to Protocol for CEF-97-006 Amd. No. 2; Investigators
8/8/2000	FDA/TAP	(IND Amendment 116) IND Safety Report - Follow-up #1
8/23/2000	FDA/TAP	(IND Amendment 117) IND Safety Report - Follow-up #2
8/30/2000	FDA/TAP	(IND Amendment 118) New and/or Revised Investigators for Mulitple Protocols
9/12/2000	FDA/TAP	(IND Amendment 119) Request for Protocol Review: Study CEF-00-034 Cefditoren vs. Levaquin
9/29/2000	FDA/TAP	(IND Amendment 120) 2000 Annual Report
10/2/2000	FDA/TAP	(IND Amendment 121) New and/or Revised Investigators for Mulitple Protocols
11/1/2000	FDA/TAP	(IND Amendment 122) New and/or Revised Investigators for Mulitple Protocols
11/15/2000	FDA/TAP	(IND Amendment 123) IND Safety Report-Follow-up #2
12/1/2000	FDA/TAP	(IND Amendment 124) New and/or Revised Investigators for Mulitple Protocols
12/29/2000	FDA/TAP	(IND Amendment 125) New and/or Revised Investigators for Mulitple Protocols
1/23/2001	FDA/TAP	(IND Amendment 126) Clinical - Study Report CEF-97-002 Cross Reference Letter
2/1/2001	FDA/TAP	(IND Amendment 127) New and/or Revised Investigators for CEF-97-006
2/5/2001	FDA/TAP	(IND Amendment 128) Update Section 7.2.1 (Name and Address of Manufacturer) of original IND
3/1/2001	FDA/TAP	(IND Amendment 129) Revised Investigators for CEF-97-006
4/2/2001	FDA/TAP	(IND Amendment 130) Revised Investigators for CEF-97-006
5/1/2001	FDA/TAP	(IND Amendment 131) Revised Investigators for CEF-97-006
7/2/2001	FDA./TAP	(IND Amendment 132) Revised Investigators for CEF-97-006

Chronology for NDA 21, 222 (Spectracef Tablets)		
Date	**To/From**	**Subject**
12/28/1999	FDA/TAP	Original submission of NDA.
12/30/1999	FDA/TAP	Telephone call to Project Manager to confirm receipt of NDA
1/4/2000	TAP/FDA	Telephone call from Project Manager stating the Division's receipt of the requisite volumes; FDA request of additional copies of certain NDA volumes; TAP described the contents of the electronic NDA that would be provided by 2/1/00
1/5/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 1/4/2000: Additional copies of certain NDA volumes
1/5/2000	TAP/FDA	Telephone call from Randy Levin to obtain clarity regarding the electronic media included in the NDA and the data-CANDA
1/6/2000	FDA/TAP	Telephone call to Randy Levin to discuss the electronic data sets to be submitted in the data-CANDA
1/10/2000	TAP/FDA	Telephone call from Dr. Shetty requesting the location of the Method Validation package and the facility contact names (and registration numbers) in the NDA
1/10/2000	FDA/TAP	Letter to Dr. Shetty containing the facility establishment numbers for the companies involved in the manufacture, control, testing, and packaging
1/11/2000	FDA/TAP	Telephone call to Project Manager inquiring if Dr. Shetty was able to find the Methods Validation Package and confirming the Division's request for stability data in Excel format
1/12/2000	TAP/FDA	Telephone from Dr. Shetty to clarify the role of Lilly del Caribe and the address of the Meiji manufacturing site
1/12/2000	FDA/TAP	Letter to Dr. Shetty containing the full address of the Meiji manufacturing site and the relationship between Ceph International and Lilly del Caribe
1/12/2000	FDA/TAP	Fax to Dr. Shetty of telephone minutes from 12/14/99 regarding the proper location of deferral from pediatric studies in the NDA
1/12/2000	TAP/FDA	Telephone call from Dr. Shetty regarding the addresses and registration information for Meiji's Gifu plant and Ceph International
1/18/2000	FDA/TAP	Telephone call to Drug Listing Office inquiring about the registration information for the Meiji Gifu plant and Ceph International
1/18/2000	TAP/FDA	Telephone calls from Project Manager regarding the location of the Environmental Assessment in the NDA and to clarify Dr. Shetty's confusion about the registration information for Meiji's Gifu plant and Ceph International
1/27/2000	TAP/FDA	Letter acknowledging the receipt of the NDA for Spectracef
1/28/2000	FDA/TAP	(NDA Amendment 001) PDF versions of volumes submitted with original NDA plus several review aids
1/28/2000	FDA/TAP	Telephone call to Project Manager inquiring if there were any outstanding issues, contents of 4-month Safety Update, and the timing of an updated stability report

Date	To/From	Subject
2/2/2000	TAP/FDA	Telephone call from Project Manager confirming the Division's receipt of the electronic media submission of 1/28/00 and requesting the establishment of a confidential e-mail link between Donna Helms and Project Manager
2/3/2000	TAP/FDA	Telephone call from Dr. Mathew Thomas requesting information about investigators in order to initiate inspection process
2/8/2000	TAP/FDA	Telephone call from Randy Levin stating that the CD-ROMs supplied to the FDA were not properly formatted for archiving
2/9/2000	FDA/TAP	(Desk Copy to DSI) Response to Dr. Thomas' telephone request on 2/3/2000: Investigator listings and Audit/Monitor Information
2/9/2000	TAP/FDA	Telephone call from Project Manager stating that the FDA was missing certain volumes of the NDA
2/10/2000	TAP/FDA	Telephone call from Project Manager following up from call on 2/9/2000 stating that the statistical reviewers had lost the volumes and requested additional copies be sent
2/10/2000	FDA/TAP	Telephone call to Randy Levin to follow-up on communications from 1/5/2000, 1/6/2000, and 2/9/2000
2/10/2000	FDA/TAP	(NDA Amendment 002) Response to telephone call on 2/8/2000: SAS Transport Files: CRFs for ISE and ISS - Studies 009 and 011
2/11/2000	FDA/TAP	Telephone call to Project Manager to confirm that the NDA was fileable
2/11/2000	TAP/FDA	Telephone call from Project Manager inquiring about the location of certain items within the NDA, safety information in the ISS, and a request to reformat data from skin studies
2/11/2000	TAP/FDA	Fax from Project Manager containing an example of how the data for the skin studies should be reformated
2/11/2000	FDA/TAP	(General Correspondence) Letter fulfilling request on 2/11/00 to clarify the information contained in the ISS
2/14/2000	FDA/TAP	(Desk Copy) Additional copies of NDA volumes missing as per the request of 2/10/2000
2/14/2000	TAP/FDA	Letter from FDA stating the FDA will be performing method validation studies on Spectracef and requesting the appropriate materials/documents to do so
2/15/2000	TAP/FDA	Letter pre-announcing the inspection of Meiji Seika Kaisha's Gifu plant
2/16/2000	FDA/TAP	Telephone call to Dr. Thomas to confirm his receipt of the submission made on 2/9/00; Dr. Thomas requested a copy of the summary for each pivotal clinical study and monitor site reports for certain investigators
2/16/2000	FDA/TAP	(Desk Copy to DSI) Respose to Dr. Thomas' Request of 2/16/00: Summaries for Pivotal Clinical Studies
2/16/2000	FDA/TAP	Telephone call to Project Manager regarding 356h, electronic media, and data presentation
2/16/2000	FDA/TAP	Telephone call to Project Manager inquiring whether the facility address for Ceph had been entered into the computer at the FDA

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2/16/2000	FDA/TAP	Telephone call to Project Manager to confirm receipt of the submission made on 2/14/00; FDA response to TAP's request for the content of the Safety Update
2/16/2000	FDA/TAP	Telephone call to NDA Coordinator at Philadelphia Pharmaceutical Laboratory regarding the HPLC column used for cefditoren assay and related substances method
2/17/2000	FDA/TAP	(Desk Copy) Response to FDA Request of 2/11/00: Reformatted tables for clinical cure rate by baseline diagnosis - Studies CEF-97-009 and CEF-97-011
2/21/2000	FDA/TAP	Telephone Call to International Inspections Group regarding the proposed inspection dates/ arrangements for the Meiji facility
2/22/2000	TAP/FDA	Telephone call from NDA Coordinator at Philadelphia Pharmaceutical Laboratory requesting reagents for cefditoren ID test
2/22/2000	FDA/TAP	(Desk Copy) Response to DSI Request of 2/16/00: Monitoring reports for specific investigators and studies
2/23/2000	FDA/TAP	Telephone call to Dr. Thomas to confirm his receipt of the submission made on 2/22/00; discussion of the submission of audit reports and conversation documentation
2/23/2000	FDA/TAP	Telephone call to Project Manager following up as to whether the facility address for Ceph had yet been entered into the computer at the FDA
2/24/2000	FDA/TAP	Letter to NDA Coordinator at Philadelphia Pharmaceutical Laboratory providing a status update on the materials requested for method validation
2/28/2000	FDA/TAP	(Desk Copy to DSI) Response to FDA Request of 2/23/00: Site Audit Reports
2/29/2000	FDA/TAP	Telephone call to Project Manager checking to see whether the facility address for Ceph had been entered into the computer at the FDA
2/29/2000	TAP/FDA	Telephone Call from International Inspections Group about FDA travel arrangements for Meiji Seika Kaisha inspection
3/1/2000	TAP/FDA	Telephone call from Project Manager to confirm that the Ceph's facility address was entered into the FDA system
3/6/2000	TAP/FDA	Telephone call from Dr. Thomas requesting patient information and data for several investigator sites
3/6/2000	FDA/TAP	Telephone call to Dr. Thomas to regarding the information requested on 3/6/2000 for the purposes of inspection
3/7/2000	FDA/TAP	Fax to Dr. Shetty containing a revised TOC for Section 4 of the NDA
3/8/2000	FDA/TAP	Fax to International Inspections Group containing the flight and hotel arrangements for the FDA in Japan
3/9/2000	FDA/TAP	Telephone call to Dr. Thomas requesting clarity on the format of the data requested on 3/6/2000
3/9/2000	TAP/FDA	Telephone call from NDA Coordinator at Philadelphia Pharmaceutical Laboratory confirming receipt of all requested materials for method validation
3/10/2000	FDA/TAP	Telephone call to Project Manager regarding CRFs in PDF format that FDA will be requesting at a future date

Date	To/From	Subject
3/13/2000	TAP/FDA	Telphone call from Statistical Reviewer regarding the organization of the datasets and the location of the dataset index
3/13/2000	FDA/TAP	Telephone call to Statistical Reviewer to clarify the dataset requests
3/17/2000	FDA/TAP	(Desk Copy to DSI) Response to FDA Request of 3/6/2000: Patient information and data for several investigator sites
3/20/2000	FDA/TAP	Fax to International Inspections Group containing the final FDA travel arrangements for the Meiji inspection
3/22/2000	FDA & TAP	Teleconference with Statistical Reviewers to clarify requests made on 3/10/2000 and 3/13/2000 related to Case Report Forms and SAS programs
3/22/2000	FDA/TAP	(Desk Copy) Response to FDA Request of 3/22/00: List of Sites excluded from analysis in NDA and text of SAS program excluding sites from ISE dataset
3/27/2000	TAP/FDA	Telephone call from Dr. Shetty verfiying Meiji's correct address
3/27/2000 - 3/29/2000		Inspection of Meiji Seika Kaisha's Gifu Plant
3/28/2000	FDA/TAP	(NDA Amendment 003) Response to FDA Request on 3/27/2000: Code Lists for the ISS and the ISE
3/28/2000	TAP/FDA	Fax from Project Manager requesting CRFs (in PDF format) for 660 patients from Phase III clinical studies
3/29/2000	TAP/FDA	Telephone call from Dr. Shetty inquiring about the location of the stability and specifications information in the NDA
3/31/2000	FDA/TAP	(NDA Amendment 004) Response to Teleconference held on 3/22/2000: Annotated CRFs for ISS and ISE
3/31/2000	TAP/FDA	Telephone call notifying TAP of inspection of first clincal site during the first week of May
4/11/2000	FDA/TAP	(NDA Amendment 005) Response to FDA Request on 3/28/2000: CRFs in PDF format for ISE and ISS - Studies 008 and 010
4/11/2000	TAP/FDA	Fax from Project Manager containing an example of a microbiology table of contents for electronic submissions to assist the reviewer in the location of each section in the NDA
4/11/2000	TAP/FDA	Fax from Project Manager containing a copy of the Division's official minutes from the teleconference held on 3/22/2000
4/11/2000	TAP/FDA	Fax from Project Manager containing Biopharm Request for PDF files, location of documents in NDA, and data file/control codes for population PK analyses
4/12/2000	FDA/TAP	(NDA Amendment 006) Response to Teleconferenece held on 3/22/00: SAS Programs for AMS data in ISE
4/18/2000	FDA/TAP	Telephone call to Randy Levin to discuss the electronic submission of 4/11/2000 and future electronic submissions
4/19/2000	TAP/FDA	Telephone call from Project Manager requesting additional micro information in electronic format; TAP's response was that most of the information had previously been submitted in electronic format but the company would be willing to resubmit the requested information

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4/24/2000	TAP/FDA	Telephone call from Project Manager stating that there was no need to resubmit the microbiology information the Agency requested on 4/19/2000
4/24/2000	FDA/TAP	(NDA Amendment 007) Response to FDA Request on 3/28/00: CRFs in PDF format for ISE and ISS - Studies 009 and 011
4/27/2000	FDA/TAP	(NDA Amendment 008) Response to Teleconference held on 3/22/2000: SAS Programs for Phase III Studies used for ISS and ISE
4/27/2000	TAP/FDA	Copy of FDA minutes from teleconference held on 3/22/2000
4/28/2000	FDA/Meiji	Letter responding to FDA written observations on Form FDA 483 from Meiji inspection (March 27-29, 2000)
4/28/2000	FDA/TAP	(Desk Copy) Development Study for Swab Sampling and Revised SOP
4/28/2000	FDA/TAP	(NDA Amendment 009) 4-Month Safety Update
4/28/2000	FDA/TAP	Letter to Puerto Rico FDA District Office: Development Study for Swab Sampling and Revised SOP
5/1/2000	FDA/TAP	(NDA Amendment 010) Notification of TAP Name & Address Change
5/2/2000 - 5/31/2000		Inspection at Lilly del Caribe manufacturing facility
5/2/2000	FDA/TAP	(Desk Copy) Copy of PK/Biopharm electronic review aid plus MS word docs for all Phase I studies, including the Drug Metabolism Reports requested via facsimile on April 28, 2000
5/3/2000	FDA/TAP	(NDA Amendment 011) Response to FDA Fax of 3/28/00: CRFs in PDF format for ISE and ISS - Studies 003, 005, 004 and 007
5/3/2000	FDA/TAP	(Desk Copy to DSI) Response to questions on audit report for two investigators
5/4/2000	TAP/FDA	Telephone call from Pharm/Tox reviewer requesting documents in Microsoft Word
5/5/2000	FDA/TAP	Telephone call to Pharm/Tox reviewer clarifying the request for reports in Word format
5/5/2000	FDA/TAP	(Desk Copy) Response to FDA Requests on 5/4/2000 and 5/5/2000: Copies of electronic review aid containing Overall and Section Reviews in MS Word format
5/10/2000	FDA/TAP	Letter to Puerto Rico FDA District Office containing Meiji Seika Kaisha's responses to the observations listed on the 483 issued 3/29/2000
5/11/2000	FDA/TAP	Telephone call to Project Manager to discuss the requests of the Pharm/Tox Reviewer made on 5/4/2000 and 5/5/2000
5/18/2000	TAP/FDA	Telephone call from Project Manager requesting multiple volumes of NDA in MS Word format for clinical and statistical reviewers
5/18/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 5/18/2000: Additional copies of reports in Microsoft Word format
5/19/2000	FDA/TAP	Telephone call to Project Manager informing him of changes in manufacturing facility
5/19/2000	FDA/TAP	(NDA Amendment 012): Updated Location of Operations Document to change from Ceph to Lilly as drug product manufacturer

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5/19/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 5/18/2000: Copies of clinical reports in Microsoft Word format
5/23/2000	TAP/FDA	Letter requesting efficacy and safety analyses on clinical studies for studies (including data from investigators originally omitted)
5/26/2000	FDA/TAP	Telephone call to FDA Chemist in Puerto Rico FDA District Office for the results of method validation testing
5/30/2000	FDA/TAP	(NDA Amendment 012): Proposed Pediatric Study Request
5/30/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 5/18/2000: Phase III Reports with Tables in MS Word Format
5/31/2000	FDA/TAP	(NDA Amendment 013) Pediatric Development Plan for cefditoren pivoxil
5/31/2000	FDA/TAP	Telephone call to Project Manager requesting additional information on letter from Agency dated 5/23/2000
5/31/2000	FDA/TAP	Telephone call to Project Manager regarding stability and status of various reviews
6/2/2000	TAP/FDA	Letter acknowledging receipt of submission on 5/1/2000 regarding sponsor name and address change
6/5/2000	TAP/FDA	Telephone call from Dr. Thomas requesting additional information about audit reports submitted on 2/28/2000
6/5/2000	TAP/FDA	Telephone call from Project Manager requesting CRFs from Study 009 and Gram Stain processing information
6/5/2000	FDA/TAP	Telephone call to Project Manager to ensure change to Lilly as manufacturer has been entered into FDA computer system
6/6/2000	FDA/TAP	Telephone call to FDA inspector in Puerto Rico District Office informing him that Lilly as manufacturer has been entered into FDA computer system
6/6/2000	FDA/TAP	Telephone call to Project Manager to check on status of ongoing NDA reviews, confirm receipt of PPSR and Pediatric Development plan, and check on status of neonate waiver; FDA Requests micro analyses based on time above MIC-90
6/8/2000	FDA/TAP	(NDA Amendment 014) Response to FDA Request on 6/5/2000: Additional CRFs for a patient from Study 009
6/8/2000	FDA/TAP	(Desk Copy to DSI) Response to FDA Request on 6/5/2000: Additional support documentation for TAP audit report #1999005
6/12/2000	FDA/TAP	(Desk Copy to DSI) Response to FDA Request: CRFs for patients in CEF-97-003 and CEF-97-005 for requested investigators
6/12/2000	TAP/FDA	Telephone call from Project Manager requesting information and clarification about statistical analyses performed in the NDA: FDA requests a decision tree
6/13/2000	FDA/TAP	Telephone call to Project Manager to obtain clarity on request of 6/12/2000 about decision trees analysis
6/13/2000	FDA/TAP	(NDA Amendment 015) Adding PCI as a packager, revised packaging components document and Klockner DMF
6/13/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 6/5/2000: Information on pre-therapy Gram Stains for AECB studies

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6/13/2000	FDA/TAP	(NDA Amendment 016) Response to FDA Request on 5/23/00: Explanation for excluding data from specific sites & reanalysis of data including these sites
6/14/2000	FDA/TAP	Telephone call to Project Manager to clarify and discuss the microbiology request on 6/6/2000
6/14/2000	TAP/FDA	Fax from Project Manager containing comments from Microbiology Reviewer regarding TAP's analysis of data and requesting additional analyses
6/15/2000	FDA/TAP	(Desk Copy to DSI) Response to FDA Request: Follow-up to submission on 6/12/2000 - CRFs for patients in CEF-97-003 and CEF-97-005 for requested investigators
6/20/2000	TAP/FDA	Telephone call from Project Manager inquiring about marketing status in foreign countries and requesting additional information about handling of sputum samples & Gram staining procedures
6/20/2000	FDA/Lilly	Letter responding to FDA written observations on Form FDA 483 from Lilly inspection (May 2-31, 2000)
6/23/2000	Lilly/FDA	FDA Letter responding to Lilly's comments about the FDA written observations on Form FDA 483 from Lilly inspection (May 2-31, 2000)
6/26/2000	Lilly/FDA	FDA Establishment Inspection Report for Lilly inspection performed on 5/2/2000-5/31/2000
6/26/2000	FDA/TAP	(Desk Copy) Response to FDA Requests on 6/20/00: Information on handling of sputum samples and Gram staining procedures
6/26/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 6/13/2000: Decision Tree Analyses for clinical studies
6/29/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 6/21/2000: Pulse Field Gel Electrophoresis Molecular Typing
7/5/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 6/14/2000: Response to Microbiology Reviewer concerning analysis of data
7/5/2000	TAP/FDA	Fax from Project Manager: Draft Letter of Deficiency from Chemistry Reviewer
7/10/2000	TAP/FDA	Telephone call from Project Manager requesting updated stability report
7/12/2000	FDA/TAP	(NDA Amendment 017) Response to FDA Request on 5/31/2000 and 7/10/2000: Stability Update
7/14/2000	FDA/TAP	(Desk Copy) Corrections to submission made on 7/5/2000: Corrected tables in response to microbiology reviewer's comments concerning analysis of data
7/17/2000	TAP/FDA	Telephone call from Project Manager requesting additional information for Meiji's ISS and ISE as well as safety/efficacy results for Japanese Phase III studies
7/19/2000	TAP/FDA	Fax from Project Manager requesting additional annotated CRFs for bronchitis studies
7/19/2000	TAP/FDA	Telephone call from Project Manager stating that PCI had not been entered into FDA computer as alternate packager as well as discussions about microbiology submission on 7/5/2000
7/21/2000	FDA/TAP	(Desk Copy) Response to Fax on 7/5/2000: TAP's Response to Draft CMC Deficiency Letter

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7/24/2000	TAP/FDA	Telephone call from Project Manager and Medical Review Officer to follow-up on request on 7/19/2000 regarding additional annotated CRFs and inquiring about the status of TAP's pneumonia studies
7/24/2000	TAP/FDA	Telephone call from Project Manager concerning references cited in the microbiology response made on 7/5/2000
7/25/2000	FDA/TAP	(Desk Copy) Response to FDA Requests on 7/19/2000 and 7/24/2000: Additional annotated CRFs for Studies 003 and 005
7/25/2000	FDA/TAP	Telephone call to Project Manager following up on numerous issues (CMC Deficiency Letter, PCI as alternate packager, clinical review of various indications, Meiji clinical data, etc.)
7/26/2000	FDA/TAP	(Desk Copy) Update on Status of Clinical Studies for Community-Acquired Pneumonia
7/27/2000	FDA/TAP	(Desk Copy) Response to FDA Request: Additional annotated CRFs for Studies 004 and 007
7/27/2000	TAP/FDA	Letter from Medical Review Officer inquiring about protocols and blinding of Augmentin for sinusitis studies
7/31/2000	FDA/Lilly	Response to FDA Letter dated 6/23/2000 regarding FDA 483 issued on 5/31/2000
8/1/2000	FDA/TAP	Telephone call to Project Manager to touch base regarding PCI as packager, pediatric waiver and PPSR status, as well as the anticipated data for the Division to request data sets for AECB and sinusitis studies
8/2/2000	FDA/TAP	(Desk Copy) Response to FDA Letter dated 7/27/2000: Response to questions about sinusitis protocols and blinding of Augmentin
8/2/2000	TAP/FDA	Telephone call from Project Manager to discuss the biopharm reviewer's ongoing request for editable electronic documents and review process for PPSR
8/3/2000	TAP/FDA	Fax from Project Manager containing form to be completed for each study per the request of the Biopharm Reviewer
8/3/2000	FDA/TAP	(Desk Copy) Response to FDA Request: Electronic copies (MS Word) of Phase I studies including tables, listings, and DM reports
8/3/2000	TAP/FDA	Fax from Project Manager containing additional data set requests for sinusitis and bronchitis indications
8/3/2000	TAP/FDA	Fax from Project Manager requesting on-therapy variables and comments included in the datasets for sinusitis and bronchitis studies
8/8/2000	FDA/TAP	Telephone call to Project Manager to discuss the request of the Biopharm Reviewer on 8/3/2000 and the status of the clinical review process
8/8/2000	TAP/FDA	Fax from Project Manager containing Biopharm reviewer requests for assay validation reports
8/8/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 8/3/2000: SAS Transport Files containing data sets and code lists in PDF format for sinusitis and bronchitis indications [submitted again as NDA Amendment 018]

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8/9/2000	FDA/TAP	Telephone call to Project Manager confirming submission made on 8/8/2000 and inquiring about the forms requested by the biopharm reviewer on 8/3/2000; Request for SAS transport files submitted on 8/8/2000 as desk copy to be submitted as an official electronic filing
8/11/2000	FDA/TAP	Teleconference with Medical Reviewers regarding the study design for clinical comparison of cefditoren and Levoquin (IND submission of 8/1/2000); Discussion of AECB studies and FDA concerns regarding gram stain analyses, study design, PK, etc.
8/14/2000	FDA/TAP	Telephone call to Project Manager to check on outstanding issues; Request for several volumes of NDA review copy FDA could not locate
8/15/2000	FDA/TAP	(NDA Amendment 018) Response to FDA Request on 8/9/2000: SAS Transport Files containing data sets and code lists in PDF format for sinusitis and bronchitis indications - resubmitted in archival format
8/15/2000	FDA/TAP	(Desk Copy) Response to FDA Biopharm Request on 8/3/2000: Reformatted summary sheets for PK/Biopharm references
8/16/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 8/15/2000: Additional volumes from clinical section of NDA
8/18/2000	FDA/PCI	Telephone call regarding the blister packaging, production schedule, and validation runs
8/18/2000	FDA/TAP	Letter to DDMAC requesting advice and comment to assist in developing launch materials
8/22/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 8/8/2000: Biopharm response concerning Assay Validation Reports
8/22/2000	FDA/TAP	Telephone call to Project Manager following up on numerous issues and requesting teleconference to clarify issues from 8/11/2000 teleconference
8/23/2000	TAP/FDA	Telephone call from Project Manager requesting a teleconference regarding the outcome information for the USSI studies
8/25/2000	TAP/FDA	Teleconference with Medical Reviewers to discuss possible reanalysis for USSI and pharyngitis studies
8/25/2000	TAP/FDA	Fax from Project Manager containing comments from Medical Reviewer regarding teleconference held on 8/25/2000
8/30/2000	FDA/TAP	Telephone call to Project Manager to discuss the process surrounding the finalization of the chemistry deficiency list
8/31/2000	FDA/TAP	(NDA Amendment 019) Response to FDA Request on 8/25/2000: Reanalysis of data from pharyngitis and USSI studies
9/5/2000	TAP/FDA	Fax from Project Manager containing biopharm request for data from PK studies CEF-013, 016, 017, and 024
9/5/2000	TAP/FDA	Fax from Project Manager containing biopharm request for studies 6952-823/5R and 823/11-1010 containing assay validation data
9/6/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 8/11/2000: Issues concerning AECB Studies such as Gram stain analyses, pre-exacerbation signs and symptoms, and statistical analyses

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9/6/2000	FDA/TAP	Telephone call to International Inspections Group requesting a copy of the EIR for the Meiji inspection and discussion of Meiji's response to Form FDA 483
9/7/2000	TAP/FDA	Fax from Project Manager containing request for histograms
9/7/2000	FDA/TAP	(Desk Copy) Response to FDA Request on September 7, 2000: Resubmission of CD-ROM containing Phase III Study Reports in MS Word Format
9/8/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 9/5/200 via telephone: Data sets from PK Studies 013, 016, 017 and 024 in MS Excel Format
9/8/2000	FDA/TAP	(Desk Copy) Response to FDA Microbiology Request on 9/5/2000: Information concerning the Reference List
9/11/2000	TAP/FDA	Fax from Project Manager containing biopharm request for data from PK studies CEF-023, 030, 015, and 018
9/11/2000	FDA/TAP	(NDA Amendment 020) Response to FDA Request on 9/5/00: Assay Validation Reports for 6952-823/5R and 823/11-1010
9/11/2000	TAP/FDA	Telephone call from Project Manager requesting data sets for - 023, 030, 015, and 018 (biopharm reviewer request) as well as data tables for CEF-97-005 (medical reviewer request)
9/13/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 9/11/2000: Data tables from Study CEF-97-005
9/13/2000	TAP/FDA	Telephone call from Project Manager requesting clarification on the references listed in the annotated labeling
9/13/2000	TAP/FDA	Telephone call from Project Manager stating that FDA would not have comments on protocol for Study CEF-00-034 until late October
9/14/2000	FDA/TAP	Telephone call to Project Manager to discuss the Division's review of the sinusitis and AECB indications
9/14/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 9/11/2000: Data sets from PK Studies 015, 018, 023 and 030 in MS Excel Format
9/14/2000	TAP/FDA	Telephone call from Project Manager and Biopharm reviewer requesting mean and SD of MIC-90 values for each microorganism used in histograms
9/15/2000	TAP/FDA	Telephone call from Biopharm reviewer clarifying request of 9/14/2000
9/15/2000	FDA/TAP	(Desk Copy) Response to Teleconference held on 8/25/2000: SAS programs used for USSI reanalysis
9/20/2000	TAP/FDA	Fax from Project Manager containing the Chemistry Deficiency List
9/21/2000	TAP/FDA	Fax from Project Manager containing biopharm requests for information on plasma and urine samples
9/21/2000	FDA & TAP	Teleconference with Medical Reviewers to discuss the primary medical review for the sinusitis indication
9/21/2000	TAP/FDA	Telephone call from Project Manager requesting a copy of the proposed label in MS Word Format
9/25/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 9/21/2000: Proposed Labeling in MS Word Format
9/26/2000	FDA/TAP	(NDA Amendment 021) Microbiology Reports and Publications received since NDA filing

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9/26/2000	FDA/TAP	(Desk Copy) Response to Teleconference held on 9/21/2000: Reanalysis of Adverse Events in ISS
9/26/2000	TAP/FDA	Fax from Medical Officer containing comments and questions regarding microbiology tables and clinical micro correlates
9/27/2000	FDA/TAP	(Desk Copy) Response to FDA Request on 9/27/2000: Hard copies of selected Case Report Forms previously submitted [previously submitted in Amendment No. 011]
9/27/2000	FDA/TAP	Telephone call to Project Manager and Medical Reviewer regarding FDA's reanalysis of AECB data and scheduling of teleconference to discuss the AECB indication
9/28/2000	FDA/TAP	(Desk Copy) Response to Teleconference held on 9/21/2000: Reanalysis of data involoving shifts in values from pretreatment to posttreatment
9/28/2000		FDA Inspection of PCI Services (Pre-approval inspection for Spectracef) - no FDA 483 issued
10/2/2000	TAP/FDA	Fax from Project Manager requesting additional calculations for CEF 97-015 and 97-018 for biopharm reviewer
10/2/2000	TAP/FDA	Fax from Project Manager containing: biopharm request regarding CEF-017 and analysis related to gender/race; FDA's clinical and micro responses from reanalysis of AECB data discussed on 9/27/2000
10/3/2000	TAP/FDA	Fax from Project Manager containing biopharm request for dosage adjustment in renal impairment patients
10/3/2000	TAP/FDA	Fax from Project Manager containing comments and questions regarding MRSA
10/3/2000	FDA/TAP	Telephone call to Project Manager confirming the receipt of faxes on 10/2/2000, obtaining clarification about the clinical micro correlates fax, and requesting teleconference to discuss Division's review of AECB indication
10/4/2000	FDA/TAP	Telephone call to Project Manager to inform him of TAP's status in responding to the multiple biopharm requests and discussion of scheduling teleconference about AECB indication
10/5/2000	FDA/TAP	(NDA Amendment 022) Response to FDA fax on 9/20/2000: CMC Information Request Letter Responses
10/10/2000	FDA/TAP	Telephone call to Project Manager to check on the status of the meeting scheduled for 10/12/2000 about the AECB indication
10/11/2000	FDA/TAP	(NDA Amendment 023) Response to FDA Request on 9/14/2000: Histograms for List 2 organisms
10/11/2000	FDA/TAP	(NDA Amendment 024) Response to Division's concerns related to Gram stains, statistical equivalence, clinical response, etc for AECB indication
10/11/2000	TAP/FDA	Telephone call from Team Leader stating the meeting for the AECB indication would be rescheduled for 10/20/2000 and discussion of meeting schedule
10/11/2000	FDA/TAP	Telephone call to Project Manager to confirm meeting time on 10/20/2000
10/12/2000	FDA/TAP	(NDA Amendment 025) Response to FDA Biopharm Requests on 9/21/2000 and 10/2/2000: Plasma and urine storage and stability; discrepancy between urinary excretion of pivalic acid between reports

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10/13/2000	TAP/FDA	Fax from Project Manager containing biopharm request related to ESRD patients in CEF-017
10/13/2000	FDA/TAP	(NDA Amendment 026) Response to FDA Request on 10/3/2000: Answers to questions related to MRSA and MSSA
10/16/2000	FDA/TAP	Telephone call to Project Manager inquiring about the agenda for the 10/20/2000 meeting; FDA Request for lists of official correspondence submissions and desk copy submissions for NDA 21,222
10/16/2000	FDA/TAP	(NDA Amendment 027) Response to FDA Biopharm Requests on 10/2/2000 and 10/3/2000: Rationale for dosage adjustment in renal impairment patients; Data calculations for Study 015 and Study 018; and Chromatograms for Renal Impairment study; reanalysis of gender data; reanalysis of gender data from studies 016 and 018
10/16/2000	FDA/TAP	Fax to Project Manager containing response to FDA Request on 10/16/2000: Lists of official correspondence and desk copy submissions for NDA 21, 222
10/17/2000	FDA/TAP	Fax to Project Manager containing corrections to fax sent on 10/16/2000
10/17/2000	FDA/TAP	Telephone call to Project Manager inquiring about the agenda for the 10/20/2000 meeting: FDA response that AECB, MRSA, and labeling would be discussed
10/17/2000	FDA/TAP	(NDA Amendment 028) Response to FDA Biopharm Request on 10/13/2000: ESRD Patients in CEF-017
10/17/2000	TAP/FDA	Fax from Project Manager containing Agenda for FDA Meeting on 10/20/2000
10/18/2000 - 11/8/2000	TAP & FDA	GMP inspection of Ceph International Manufacturing facility
10/18/2000	TAP/FDA	Fax from Project Manager containing FDA Attendees for FDA Meeting on 10/20/2000
10/18/2000	FDA/TAP	Fax to Project Manager in Response to FDA Request: Lots of drug product manufactured at Meiji and Lilly
10/19/2000	FDA/TAP	Fax to Project Manager in Response to FDA Request: Information about Lots used to dose patients in clinical studies
10/19/2000	TAP/FDA	FDA Comments on proposed package insert for Spectracef tablets
10/20/2000	TAP & FDA	Meeting between TAP and Reviewing Division to discuss AECB indication, MRSA, and labeling
10/25/2000	TAP/FDA	Telephone call from Project Manager requesting the withdrawal of the sinusitis indication and listing information provided in FDA annotated labeling
10/25/2000	TAP/FDA	Telephone call from Dr. Thomas requesting CRFs for Dr. Aldrich's patients in CEF-97-007 and -011
10/25/2000	FDA/TAP	(NDA Amendment 029) Withdrawal of Sinusitis Indication
10/26/2000	FDA/TAP	(NDA Amendment 030) Response to FDA Labeling Comments on 10/19/2000: Information on serum carnitine and laboratory parameters
10/26/2000	TAP/FDA	Telephone call from Dr. Thomas inquiring about the location of the original X-rays from Dr. Aldrich's site

Date	To/From	Subject
10/27/2000	TAP/FDA	Fax from Project Manager containing the Division's attendees from the meeting on 10/20/2000
10/27/2000	TAP/FDA	FDA Action Letter for Spectracef tablets
10/27/2000		Teleconference to discuss the approvable letter and the AECB indication
10/31/2000	FDA/TAP	(NDA Amendment 031) TAP's notification in response to approvable letter informing Agency of intent to amend the NDA
11/1/2000	FDA/TAP	(Desk Copy to DSI) Response to FDA Request on 10/25/2000: Case Report Forms and Enrollment Log for Dr. Aldrich
11/2/2000	TAP/FDA	Telephone call from Dr. Thomas requesting written statement documenting the location of X-Rays from Dr. Aldrich's site
11/6/2000	TAP/FDA	Electronic files in MS Word format for FDA version of proposed package insert for Spectracef tablets
11/6/2000	TAP/FDA	Fax from Project Manager containing microbiology request for further information and clarification regarding submissions made on 7/5/2000, 10/11/2000, 10/13/2000, and in the NDA [TAP's response included in Amendment 032]
11/7/2000	FDA/TAP	Telephone call to Project Manager to discuss the scheduling of the teleconference on BE study in fasted subjects
11/8/2000	FDA/TAP	Telephone call to Project manager requesting meetings with Division to discuss TAP's AECB reanalysis plan and FDA's requested BE study
11/8/2000	FDA/TAP	Fax to Project Manager requesting teleconferences for AECB reanalyses according to Winnipeg criteria and bioequivalence study in fasted subjects
11/8/2000	FDA/TAP	E-mail to Project Manager requesting dates for teleconferences on AECB reanalyses and BE study
11/8/2000	FDA/TAP	(Desk Copy) Response to FDA approvable letter and teleconference on 10/27/2000: TAP Plan for Reanalysis of AECB data
11/9/2000	FDA/TAP	Telephone call to Dr. Thomas to update him on actions being taken to provide written statement on location of X-rays for Dr. Aldrich's site
11/13/2000	TAP/FDA	Telephone call from Project Manager postponing the scheduled teleconference regarding the reanalyses of AECB data
11/13/2000	FDA/TAP	Telephone call to the Drug Listing Office in regards to foreign establishment, FDA Form 2656, and FDA Form 2657
11/15/2000	TAP/FDA	Telephone call from Project Manager stating that the date and times for the teleconferences regarding AECB reanalysis and bioequivalence study
11/15/2000	TAP/FDA	Telephone call to Project Manager stating that the secure e-mail process works; Request from medical reviewer relating to abnormal laboratory results in labeling
11/15/2000	FDA/TAP	Telephone call to Project Manager confirming the teleconference for the AECB analyses and requesting discussion of the BE study at that same teleconference
11/15/2000	TAP/FDA	E-mail from Project Manager requesting agenda for BE study discussion
11/15/2000	FDA/TAP	E-mail to Project Manager containing agenda for BE study discussion

Date	To/From	Subject
11/16/2000	TAP/FDA	Telephone call from Project Manager stating that the FDA will be unable to discuss the BE study at the 11/17/2000 teleconference; FDA requested clarification on TAP's clinical supplies concern for the BE study
11/16/2000	TAP/FDA	E-mail from Project Manager containing biopharm request for fat content and total caloric content of meals for a completed BE study
11/16/2000	FDA/TAP	(Desk Copy to DSI) Response to FDA Request on 11/2/2000: Written Statement regarding location of X-rays from Dr. Aldrich's Site
11/17/2000	TAP/FDA	Telephone call from Dr. Thomas confirming receipt of submission on 11/16/2000; Request for documentation that confirms Dr. Aldrich's receipt of X-rays from FedEx
11/17/2000	FDA/TAP	Telephone call to Dr. Thomas requesting clarification on request made 11/17/2000
11/17/2000		Teleconference between TAP and Division to discuss reanalysis of AECB data
11/20/2000	TAP/FDA	E-mail from Project Manager containing biopharm request for fat content and total caloric content of meals for study 823/2
11/20/2000	FDA/TAP	(NDA Amendment 032) Revised Draft Labeling for Spectracef tablet
11/21/2000	FDA/TAP	E-mail response to FDA Request on 11/20/2000: Fat content and total caloric content of meals for 823/2
11/21/2000	TAP/FDA	Telephone call from Project Manager requesting list of lots that could be used in the BE study proposed by FDA
11/22/2000	FDA/Ceph	Letter responding to FDA written observations on Form FDA 483 from Ceph inspection (October 18-November 8, 2000)
11/27/2000	FDA/TAP	Fax response to FDA Request on 11/21/2000: List of lots that could be used in BE study proposed by FDA
11/27/2000	TAP/FDA	Telephone call from Project Manager requesting a list of which lot of drug has been used to dose each patient in clinical studies 003 and 005
11/28/2000	FDA/TAP	Fax to Project Manager in response to FDA Request on 11/28/2000: List of lots used to dose patients in 003 and 005
11/29/2000	TAP/FDA	Telephone call from Project Manager to discuss the expiration date of the lots provided in the fax on 11/28/2000
11/29/2000	Meiji/FDA	Letter classifying Meiji's manufacturing facility as acceptable relative to GMPs
11/29/2000	FDA/TAP	Telephone call to Project Manager regarding request for teleconference to discuss BE study proposed by the FDA and discussion of lots to be used in the study
12/1/2000	TAP & FDA	Teleconference with Project Manager to discuss BE study
12/1/2000	TAP/FDA	E-mail from Project Manager requesting manufacturing and expiration dates for Japanese lots
12/1/2000	TAP/FDA	Telephone call from Project Manager requesting paddle speed for lots in dissolution report
12/1/2000	TAP/FDA	E-mail from Project Manager requesting dissolution profiles for all lots that have 3 or more months remaining before expiry

Date	To/From	Subject
12/4/2000	FDA/TAP	E-mail to Project Manager regarding available lots within expiry for Meiji or Lilly product and request for teleconference regarding BE study
12/4/2000	TAP/FDA	Fax from Project Manager containing Division's comments regarding proposed AECB clinical study
12/5/2000	TAP/FDA	Telephone call from Project Manager to provide the date, time, and FDA attendees for the teleconference regarding proposed BE study
12/8/2000	TAP/FDA	Telephone call from Project Manager and Biopharm reviewers requesting clarification on manufacturing and expiration for lots to be used in proposed BE study
12/8/2000	FDA/TAP	E-mail to Project Manager in response to FDA request on 12/8/2000: Manufacturing information and expiration dates for lots to be used in proposed BE study
12/14/2000	TAP/FDA	Telephone call from Project Manager requesting the composition of the formulation for two lots of drug
12/14/2000	FDA/TAP	Fax in response to FDA Request on 12/14/2000: Composition of formulation for two lots
12/14/2000	FDA/TAP	Telephone call to Dr. Thomas updating him on the new information received about the location of the X-rays for Dr. Aldrich's site
12/15/2000		Teleconference between TAP and Division to discuss BE study in fasted state proposed by FDA
12/15/2000	FDA/TAP	(Desk Copy to DSI) Response to FDA Request on 11/17/2000: Supportive Documentation for Aldrich X-rays
12/15/2000	TAP/FDA	E-mail from Project Manager requesting complete formulation for Lot D-40184 including solvents
12/26/2000	FDA/TAP	E-mail to Project Manager in response to FDA request on 12/15/2000: Comparison of manufacturing formulas for three lots used in BE studies
12/28/2000	FDA/TAP	Telephone call to Project Manager regarding status of labeling review, ISS content, and abnormal labs placement in labeling
1/5/2001	TAP/FDA	Telephone call from Project Manager regarding status of labeling review and TAP's intent to submit pneumonia study instead of Winnipeg reanalysis and proposal for modified ISS
1/8/2001	FDA/TAP	E-mail to Project Manager containing update of ISS, proposed criteria for assessment of abnormal lab values, and other intended submission dates
1/8/2001	TAP/FDA	Telephone call from Project Manager to clarify intent of the pneumonia study; discussion of abnormal labs, modified ISS, and revised labeling
1/14/2001	FDA/TAP	E-mail to Project Manager regarding the proposed ISM
1/15/2001	FDA/TAP	(NDA Amendment 033) Clinical Report for Study CEF-97-002 to support AECB indication
1/15/2001	FDA/TAP	(Desk Copy) Word Files for Clinical Study Report CEF-97-002
1/23/2001	FDA/TAP	Telephone call to Project Manager about status of FDA response to TAP's proposed ISS and ISM
1/24/2001	TAP/FDA	E-mail from Project Manager containing request from Microbiology reviewer for zone size vs MIC for pre-clinical data and comments on the proposed ISM

Date	To/From	Subject
1/24/2001	FDA/TAP	(Desk Copy) Datasets, programs, and macros used in analysis of study CEF-97-002
1/26/2001	TAP/FDA	E-mail from Project Manager containing comments from Medical Reviewer on TAP's Proposed ISS
1/29/2001	FDA/TAP	Telephone call to Project Manager regarding proposed ISS comments, FDA comments on second draft of proposed labeling, and anticipated date of FDA request for CRFs from CEF-97-002
1/29/2001	FDA/TAP	E-mail to Project Manager regarding abnormal laboratory values for cefdinir and source of criteria for abnormal lab values
1/31/2001	TAP/FDA	E-mail from Project Manager containing randomized list of CRF's for CEF-97-002
2/5/2001	FDA/TAP	E-mail to Project Manager regarding typo in FDA e-mail dated 1/26/2001 related to clinically significant laboratory values
2/5/2001	FDA/TAP	(NDA Amendment 034) Update of Location of Operations Documents in NDA for API and Drug Product Manufacturing, Testing, and Controls
2/6/2001	TAP/FDA	E-mail from Project Manager correcting a WBC count typo related to abnormal labs
2/8/2001	FDA/TAP	(NDA Amendment 035) Response to FDA Request on 1/31/2001: Ninety Case Report Forms for CEF-97-002
2/28/2001	FDA/TAP	(NDA Amendment 036) Updated Integrated Summary of Microbiology
2/28/2001	FDA/TAP	(Desk Copy) Word Files for Updated Integrated Summary of Microbiology
3/1/2001	FDA/TAP	E-mail to Project Manager in response to Microbiology Reviewer Request on 1/24/2001
3/1/2001	FDA/TAP	(NDA Amendment 037) Updated Integrated Summary of Safety
3/1/2001	FDA/TAP	(Desk Copy) Word Files for Updated Integrated Summary of Safety
3/2/2001	FDA/TAP	Telephone call to Project Manager clarifying response to Microbiology Reviewer in the e-mail dated 3/1/2001
3/9/2001	TAP/FDA	Telephone call from Project Manager requesting the original protocol for Study CEF-97-002 for the Medical Reviewer
3/12/2001	FDA/TAP	Telephone call to Medical Reviewer providing the submission numbers and dates of protocol/protocol amendments for Study CEF-97-002 in response to request made on 3/9/2001
3/16/2001	TAP/FDA	Telephone Call from Dr. Thomas requesting Investigator Brochures during time Drs. DeAbate and Mathew were involved in clinical studies
3/16/2001	FDA/TAP	Response to Request on 3/16/2001: 1997 and 1998 Investigator Brochures
3/23/2001	FDA/TAP	Request for DDMAC Advice and Comment: Pre-clearance for SPECTRACEF packaging
3/28/2001	FDA/TAP	Telephone call to Project Manager regarding the fact that TAP has not yet received an acknowledgement letter for NDA resubmission
4/3/2001	FDA/TAP	Telephone call to Project Manager regarding status of acknowledgement letter and status of FDA review

Date	To/From	Subject
4/11/2001	TAP/FDA	Telephone call from Project Manager regarding Una Ortell's request for contact information for the chemistry reviewer
4/11/2001	FDA/TAP	Telephone to Project Manager regarding acknowledgement letter for resubmission based on FDA Guidance "Classifying Resubmissions in Response to Action Letters"; FDA Request for FDC information for Study CEF-97-002; Project Manager informed TAP that a Written Request in response to Proposed Pediatric Study Request for exclusivity will be provided at a later date
4/11/2001	TAP/FDA	Telephone call from Project Manager stating that an acknowlegement of receipt letter for resubmission was being drafted in accordance with MAPP 6020.4
4/26/2001	FDA/TAP	Telephone call to Project Manager stating TAP had not received letter of acknowledgement for resubmission, status of FDA request for FDCs from CEF-97-002, closure of second pneumonia study, and inquiring about status of FDA review of resubmission
4/27/2001	FDA/TAP	E-mail to Project Manager regarding the proposed enrollment closure date of May 15, 2001 for CEF-97-006
4/27/2001	FDA/TAP	(NDA Amendment 038) Response to FDA Request on 4/11/2001: Financial Disclosure Information for Study CEF-97-002
5/2/2001	TAP/FDA	E-mail from Project Manager containing Medical Reviewer's comments regarding the closure of CEF-97-006
5/18/2000	FDA/TAP	Telephone call to Project Manager stating TAP had not received letter of acknowledgement for resubmission and Written Request regarding pediatric exclusivity, status of validation lots, and anticipated action date
5/22/2001	FDA/TAP	Telephone call to Project Manager to schedule a teleconference with the FDA statistician regarding NDA resubmission
5/29/2001	TAP/FDA	Telephone call from Project Manager cancelling the scheduled teleconference with the statistical reviewer and stating that it could be rescheduled
6/1/2001	FDA/TAP	Telephone call to Project Manager to further discuss re-scheduling of teleconference; Voicemail message stated that the Project Manager was no longer with the Division
6/1/2001	FDA/TAP	Telephone call to Medical Reviewer to discuss the review of the NDA Resubmission (CAP Study CEF-97-002); Reviewer mentioned that he wants to do other subgroup analyses and needs to meet with the statistical reviewer in addition to having many other high priority projects
6/1/2001	FDA/TAP	Telephone call to Division Director to discuss interim Project Manager contact and target date for review completion
6/5/2001	TAP/FDA	Telephone call from new Project Manager (Beth Duvall-Miller) regarding the incorrect coding of the resubmission, new goal date of August 31, and location of latest labeling
6/6/2001	TAP/FDA	Telephone call from Project Manager and Divison Director regarding the status of the review, action date of August 31, and tentative scheduling of labeling meetings for late July or early August

Date	To/From	Subject
6/11/2001	FDA/TAP	Telephone call to Project Manager to discuss written request for pediatric exclusivity, letter of acknowledgement for resubmission, and secure e-mail
6/11/2001	TAP/FDA	Fax from Project Manager containing letter dated May 11, 2001 (TAP did not receive letter previously):FDA Response to proposed pediatric study request...FDA unable to issue a Written Request
6/11/2001	TAP/FDA	Telephone call from Project Manager regarding some proposed date for labeling review meetings
6/13/2001	FDA/TAP	(NDA Amendment 039) TAP's Content and Format Proposal for the CAP SNDA to be submitted in October or November 2001
6/19/2001	TAP/FDA	Letter from Division dated 6-11--2001 acknowledging resubmission and stating new user fee goal date of 8-31-2001
6/21/2001	FDA/TAP	Telephone call to Project Manager to discuss dates of labeling meetings, CAP SNDA proposal, and FDA Requested a copy of the minutes from the telecon held on December 15, 2000
6/22/2001	TAP/FDA	Fax from Project Manager containing FDA Response to TAP's Proposal for the CAP SNDA Format and Content
6/25/2001	TAP/FDA	Telephone call from Project Manager requesting Study CEF-97-002 in MS Word Format and Revised Labeling to Include Food Administration Directions agreed upon in December 15, 2000 teleconference, and stating FDA may request some reanalysis of CAP data
6/26/2001	TAP/FDA	Telephone call from Project Manager stating that the MS Word copies of the CEF-97-002 report were not needed as the FDA had located their copies submitted on January 15, 2001; Brief Discussion of Labeling History Comments from the Division to Assist in Informing the New Project Manager
6/26/2001	FDA/TAP	(NDA Amendment 040) Response to FDA Request on 6/25/2001: Revised Draft Labeling to Include Food Administration Directions
6/26/2001	FDA/TAP	Fax to Project Manager in Response to FDA Request on 6/21/2001: Meeting Minutes for Teleconference held on December 15, 2000
6/28/2001	TAP/FDA	Telephone call from Project Manager to schedule the time for the teleconference to be held on June 29, 2001
6/29/2001	TAP/FDA	Teleconference with the Agency in which FDA requested responses to some statistical program questions and a sensitivity analysis for CEF-97-002
7/3/2001	TAP/FDA	E-mail from Project Manager containing the request by the Agency in the June 29, 2001 teleconference
7/3/2001	FDA/TAP	E-mail to Project Manager containing the reponse to the statistical program requests discussed in the teleconference held on June 29, 2001
7/11/2001	TAP/FDA	E-mail from Project Manager requesting the names of the attendees at the June 29, 2001 teleconference and providing the names of the FDA attendees
7/12/2001	FDA/TAP	E-mail to Project Manager stating the TAP attendees at the June 29th teleconference

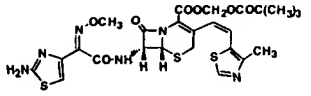
Date	To/From	Subject
7/12/2001	TAP/FDA	E-mail from Project Manager stating that she has not heard from the statistical reviewer as to whether the response provided to the Agency on July 3, 2001 was acceptable and inquiring if any of the attendees at the June 29th teleconference were doctors
7/12/2001	FDA/TAP	(NDA Amendment 041) Response to FDA Requests in June 29th teleconference and the e-mail from the Project Manager on July 3, 2001: Clinical reanalyses and statistical clarification
7/16/2001	TAP/FDA	E-mail from Project Manager containing minutes from teleconference held on November 17, 2000 and informing TAP that the labeling meeting scheduled for August 7, 2001 has been extended from 1-5 pm
7/20/2001	FDA/TAP	Fax to John Alexander of the Division containing the true microbiologic ITT population reanalyses for CEF-97-002 requested by the Agency on July 17, 2001
7/20/2001	FDA/TAP	Telephone call to Medical Review Officer to inform him of the completed ITT reanalyses and inquired whether the evaluable set of data was needed; discussions of the August 7, 2001 labeling meeting in which Dr. Alexander stated that it was the Agency's goal to finish the labeling at the meeting
7/23/2001	FDA/TAP	Fax to John Alexander of the Division containing the microbiologic evaluable population reanalyses for CEF-97-002 requested by the Agency on July 23, 2001
7/23/2001	FDA/TAP	(NDA Amendment 042) Response to Discussions with FDA on July 17-23, 2001: True Microbiologic ITT and Microbiologic Evaluable Population Reanalyses
7/25/2001	FDA/TAP	Telephone call to Project Manager to discuss logistics for the August 7, 2001 labeling meeting, timing of FDA labeling edits prior to August 7th meeting, and FDA attendees for the meeting
7/25/2001	TAP/FDA	E-mail from Proejct Manager containing final FDA meeting minutes from the August 25, 2000 and November 17, 2000 teleconferences
7/26/2001	TAP/FDA	E-mail from Project Manager requesting four submissions sent to Agency as Desk Copies be formally submitted as an amendment to the FDA
7/30/2001	FDA/TAP	Telephone call to Project Manager to discuss FDA request of July 26, 2001; Project Manager spoke of discussion within the Division regarding dosing
7/30/2001	FDA/TAP	(NDA Amendment 043) Correction of chemical name on FDA Form 356h
7/30/2001	FDA/TAP	(NDA Amendment 044) Marketing Exclusivity Claim for Cefditoren Pivoxil in the United States
7/30/2001	FDA/TAP	(NDA Amendment 045) Response to FDA Request on July 26, 2001: Formal Submission of Four Requested Desk Copies
8/1/2001	FDA/TAP	Telephone call to Project Manager to provide cell phone number in case needed for Division's internal labeling meeting
8/1/2001	TAP/FDA	Telephone call from Project Manager requesting the expiry dates for the lot numbers of drug used for the two CAP studies
8/2/2001	FDA/TAP	E-mail to Project Manager containing lost numbers and expiry periods for the drug used for two CAP studies

Date	To/From	Subject
8/2/2001	TAP/FDA	E-mail from Project Manager containing meeting minutes from teleconference held on June 29, 2001 regarding reanalyses of CAP data
8/2/2001	TAP/FDA	E-mail from Project Manager containing FDA Revised Labeling (Warnings, Indications and Dosages Sections not revised by the FDA yet)
8/2/2001	TAP/FDA	E-mail from Project Manager requesting clarification about the manufacturer TAP refers to as Ceph
8/2/2001	FDA/TAP	E-mail to Project Manager clarifying the technology transfer from Meiji to Lilly to Ceph International
8/2/2001	TAP/FDA	E-mail from Proejct Manager requesting Financial Disclosure information for studies CEF-97-008 and CEF-97-012
8/6/2001	FDA/TAP	E-mail to Project Manager containing TAP's revised labeling in response to the Division's revised labeling received on 8/2/2001
8/7/2001	FDA & TAP	Meeting to Discuss SPECTRACEF Labeling at FDA
8/8/2001	TAP/FDA	E-mail from Project Manager containing Revised Labeling Agreed Upon at the Meeting held on 08/07/2001
8/8/2001	TAP/FDA	E-mail from Project Manager containing and updated version of the draft SPECTRACEF Labeling containing new FDA revisions to the PRECAUTIONS section
8/9/2001	FDA/TAP	E-mail to Project Manager containing TAP's revisions to the latest version of the FDA labeling sent on 8/08/01
8/10/2001	FDA/TAP	(NDA Amendment 046) Financial Disclosure Information for Studies CEF-97-003, CEF-97-010, CEF-97-008, and CEF-97-012
8/10/2001	FDA/TAP	(NDA Amendment 047) Response to Meeting Held on August 7, 2001: Issues Regarding Proposed Dosing for AECB Indication
8/10/2001	FDA/TAP	Telephone call to Project Manager to confirm time of August 15, 2001 labeling teleconference, TAP's intent to submit 'position paper' regarding AECB indication, and confirmation that Ceph International is in the FDA EES system
8/10/2001	TAP/FDA	E-mail from Project Manager in reponse to Fax sent on August 2, 2001: 32 desk copies, facsimiles, or e-mail communications that the Division would want formally submitted to the Agency

DESCRIPTION

SPECTRACEF tablets contain cefditoren pivoxil, a semi-synthetic cephalosporin antibiotic for oral administration. It is a prodrug which is hydrolyzed by esterases during absorption, and the drug is distributed in the circulating blood as active cefditoren.

Chemically, cefditoren pivoxil is (-)-(6*R*,7*R*)-2,2-dimethylpropionyloxymethyl 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(*Z*)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. The empirical formula is $C_{25}H_{28}N_6O_7S_3$ and the molecular weight is 620.73. The structural formula of cefditoren pivoxil is shown below:



cefditoren pivoxil

The amorphous form of cefditoren pivoxil developed for clinical use is a light yellow powder. It is freely soluble in dilute hydrochloric acid and soluble at levels equal to 6.06 mg/mL in ethanol and <0.1 mg/mL in water.

SPECTRACEF tablets contain 200 mg of cefditoren as cefditoren pivoxil and the following inactive ingredients: croscarmellose sodium, sodium caseinate (a milk protein), D-mannitol, magnesium stearate, sodium tripolyphosphate, hydroxypropyl methylcellulose, and hydroxypropyl cellulose. The tablet coating contains hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and carnauba wax. Tablets are printed with ink containing FD&C Blue No. 1, D&C Red No. 27, shellac, and propylene glycol.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

Oral Bioavailability

Following oral administration, cefditoren pivoxil is absorbed from the gastrointestinal tract and hydrolyzed to cefditoren by esterases. Maximal plasma concentrations (C_{max}) of cefditoren under fasting conditions average 1.8 ± 0.6 µg/mL following a single 200 mg dose and occur 1.5 to 3 hours following dosing. Less than dose-proportional increases in C_{max} and area under the concentration-time curve (AUC) were observed at doses of 400 mg and above. Cefditoren does not accumulate in plasma following twice daily administration to subjects with normal renal function. Under fasting conditions, the estimated absolute bioavailability of cefditoren pivoxil is approximately 14%. The absolute bioavailability of cefditoren pivoxil administered with a low fat meal (693 cal, 14 g fat, 122 g carb, 23 g protein) is 16.1 ± 3.0%.

Food Effect

Administration of cefditoren pivoxil following a high fat meal (858 cal, 64 g fat, 43 g carb, 31 g protein) resulted in a 70% increase in mean AUC and a 50% increase in mean C_{max} compared to administration of cefditoren pivoxil in the fasted state. After a high fat meal, the C_{max} averaged 3.1 ± 1.0 µg/mL following a single 200 mg dose of cefditoren pivoxil and 4.4 ± 0.9 µg/mL following a 400 mg dose. Cefditoren AUC and C_{max} values from studies conducted with a moderate fat meal (648 cal, 27 g fat, 73 g carb, 29 g protein) are similar to those obtained following a high fat meal.

Distribution

The mean volume of distribution at steady state (V_{ss}) of cefditoren is 9.3 ± 1.6 L. Binding of cefditoren to plasma proteins averages 88% from *in vitro* determinations, and is concentration-independent at cefditoren concentrations ranging from 0.05 to 10 µg/mL. Cefditoren is primarily bound to human serum albumin and its binding is decreased when serum albumin concentrations are reduced. Binding to α-1-acid glycoprotein ranges from 3.3 to 8.1%. Penetration into red blood cells is negligible.

Skin blister fluid

Maximal concentrations of cefditoren in suction-induced blister fluid were observed 4 to 6 hours following administration of a 400 mg dose of cefditoren pivoxil with a mean of 1.1 ± 0.42 µg/mL. Mean blister fluid AUC values were 56 ± 15% of corresponding plasma concentrations.

Tonsil tissue

In fasted patients undergoing elective tonsillectomy, the mean concentration of cefditoren in tonsil tissue 2 to 4 hours following administration of a 200 mg dose of cefditoren pivoxil was 0.18 ± 0.07 µg/g. Mean tonsil tissue concentrations of cefditoren were 12 ± 3% of the corresponding serum concentrations.

Cerebrospinal Fluid (CSF)

Data on the penetration of cefditoren into human cerebrospinal fluid are not available.

Metabolism and Excretion

Cefditoren is eliminated from the plasma, with a mean terminal elimination half-life ($t_{1/2}$) of 1.6 ± 0.4 hours in young healthy adults. Cefditoren is not appreciably metabolized. After absorption, cefditoren is mainly eliminated by excretion into the urine, with a renal clearance of approximately 4-5 L/h. Studies with the renal tubular transport blocking agent probenecid indicate that tubular secretion, along with glomerular filtration is involved in the renal elimination of cefditoren. Cefditoren renal clearance is reduced in patients with renal insufficiency. (See Special Populations, *Renal Insufficiency and Hemodialysis*.)

Hydrolysis of cefditoren pivoxil to its active component, cefditoren, results in the formation of pivalate. Following multiple doses of cefditoren pivoxil, greater than 70% of the pivalate is absorbed. Pivalate is mainly eliminated (>99%) through renal excretion, nearly exclusively as pivaloylcarnitine.

Following a 200 mg BID regimen for 10 days, the mean decrease in plasma concentrations of total carnitine was 18.1 ± 7.2 nmole/mL, representing a 39% decrease in plasma carnitine concentrations. Following a 400 mg BID regimen for 14 days, the mean decrease in plasma concentrations of carnitine was 33.3 ± 9.7 nmole/mL, representing a 63% decrease in plasma carnitine concentrations. Plasma concentrations of carnitine returned to the normal control range within 7 to 10 days after discontinuation of cefditoren pivoxil. (See **PRECAUTIONS, General and CONTRAINDICATIONS.**)

Special Populations

Geriatric

The effect of age on the pharmacokinetics of cefditoren was evaluated in 48 male and female subjects aged 25 to 75 years given 400 mg cefditoren pivoxil BID for 7 days. Physiological changes related to increasing age increased the extent of cefditoren exposure in plasma, as evidenced by a 26% higher C_{max} and a 33% higher AUC for subjects aged ≥65 years compared with younger subjects. The rate of elimination of cefditoren from plasma was lower in subjects aged ≥65 years, with $t_{1/2}$ values 16-26% longer than for younger subjects. Renal clearance of cefditoren in subjects aged ≥65 years was 20-24% lower than in younger subjects. These changes could be attributed to age-related changes in creatinine clearance. No dose adjustments are necessary for elderly patients with normal (for their age) renal function.

Gender

The effect of gender on the pharmacokinetics of cefditoren was evaluated in 24 male and 24 female subjects given 400 mg cefditoren pivoxil BID for 7 days. The extent of exposure in plasma was greater in females than in males, as evidenced by a 14% higher C_{max} and a 16% higher AUC for females compared to males. Renal clearance of cefditoren in females was 13% lower than in males. These differences could be attributed to gender-related differences in lean body mass. No dose adjustments are necessary for gender.

Renal Insufficiency

Cefditoren pharmacokinetics were investigated in 24 adult subjects with varying degrees of renal function following administration of cefditoren pivoxil 400 mg BID for 7 days. Decreased creatinine clearance (CL_{cr}) was associated with an increase in the fraction of unbound cefditoren in plasma and a decrease in the cefditoren elimination rate, resulting in greater systemic exposure in subjects with renal impairment. The unbound C_{max} and AUC were similar in subjects with mild renal impairment (CL_{cr}: 50-80 mL/min/1.73 m²) compared to subjects with normal renal function (CL_{cr}: >80 mL/min/1.73 m²). Moderate (CL_{cr}: 30-49 mL/min/1.73 m²) or severe (CL_{cr}: <30 mL/min/1.73 m²) renal impairment increased the extent of exposure in plasma, as evidenced by mean unbound C_{max} values 90% and 114% higher and AUC values 232% and 324% higher than that for subjects with normal renal function. The rate of elimination from plasma was lower in subjects with moderate or severe renal impairment, with respective mean $t_{1/2}$ values of 2.7 and 4.7 hours. No dose adjustment is necessary for patients with mild renal impairment (CL_{cr}: 50-80 mL/min/1.73 m²). It is recommended that not more than 200 mg BID be administered to patients with moderate renal impairment (CL_{cr}: 30-49 mL/min/1.73 m²) and 200 mg QD be administered to patients with severe renal impairment (CL_{cr}: <30 mL/min/1.73 m²). (See **DOSAGE AND ADMINISTRATION.**)

Hemodialysis

Cefditoren pharmacokinetics investigated in six adult subjects with end-stage renal disease (ESRD) undergoing hemodialysis given a single 400 mg dose of cefditoren pivoxil were highly variable. The mean $t_{1/2}$ was 4.7 hours and ranged from 1.5 to 15 hours. Hemodialysis (4 hours duration) removed approximately 30% of cefditoren from systemic circulation but did not change the apparent terminal elimination half-life. The appropriate dose for ESRD patients has not been determined. (See **DOSAGE AND ADMINISTRATION.**)

Hepatic Disease

Cefditoren pharmacokinetics were evaluated in six adult subjects with mild hepatic impairment (Child-Pugh Class A) and six with moderate hepatic impairment (Child-Pugh Class B). Following administration of cefditoren pivoxil 400 mg BID for 7 days in these subjects, mean C_{max} and AUC values were slightly (<15%) greater than those observed in normal subjects. No dose adjustments are necessary for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). The pharmacokinetics of cefditoren in subjects with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Microbiology

Cefditoren is a cephalosporin with antibacterial activity against gram-positive and gram-negative pathogens. The bactericidal activity of cefditoren results from the inhibition of cell wall synthesis via affinity for penicillin-binding proteins (PBPs). Cefditoren is stable in the presence of a variety of β-lactamases, including penicillinases and some cephalosporinases.

Cefditoren has been shown to be active against most strains of the following bacteria, both *in vitro* and in clinical infections, as described in the **INDICATIONS AND USAGE** section.

Aerobic Gram-Positive Microorganisms

Staphylococcus aureus (methicillin-susceptible strains, including β-lactamase-producing strains)
Note: Cefditoren is inactive against methicillin-resistant *Staphylococcus aureus*
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic Gram-Negative Microorganisms

Haemophilus influenzae (including β-lactamase-producing strains)
Haemophilus parainfluenzae (including β-lactamase-producing strains)
Moraxella catarrhalis (including β-lactamase-producing strains)

The following *in vitro* data are available, but their clinical significance is unknown. Cefditoren exhibits *in vitro* minimum inhibitory concentrations (MICs) of ≤0.125 µg/mL against most (≥90%) strains of the following bacteria; however, the safety and effectiveness of cefditoren in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms

Streptococcus agalactiae
Streptococcus Groups C and G
Streptococcus, viridans group (penicillin-susceptible and -intermediate strains)

Susceptibility Tests

Dilution Techniques

Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods[1] (broth) or equivalent with standardized inoculum concentrations and standardized concentrations of cefditoren powder. The MIC values obtained should be interpreted according to the following criteria:

For testing *Haemophilus* spp.[a] and *Streptococcus* spp. including *S. pneumoniae*[b]:

Clinical Isolates	MIC (µg/mL)	Interpretation
S. pneumoniae	≤0.125	Susceptible (S)
	0.250	Intermediate (I)
	≥0.50	Resistant (R)
Haemophilus spp.	≤0.125	Susceptible (S)
	0.250	Intermediate (I)
	≥0.50	Resistant (R)
S. pyogenes	≤0.125	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Test Medium (HTM).[1]

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Streptococcus* spp. using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

Susceptibility test criteria can not be established for *S. aureus*.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control bacterial strains to control the technical aspects of the laboratory procedures. Standard cefditoren powder should provide the following MICs with these quality control strains:

Microorganisms	MIC Ranges (µg/mL)
Streptococcus pneumoniae[a] ATCC 49619	0.016 – 0.12
Haemophilus influenzae[b] ATCC 49766	0.004 – 0.016
Haemophilus influenzae[b] ATCC 49247	0.06 – 0.25

[a] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

[b] This quality control range is applicable to only *H. influenzae* ATCC 49247 and ATCC 49766 tested by a microdilution procedure using HTM.[1]

INDICATIONS AND USAGE

SPECTRACEF is indicated for the treatment of mild to moderate infections in adults and adolescents (12 years of age or older) which are caused by susceptible strains of the designated microorganisms in the conditions listed below.

Acute Bacterial Exacerbation of Chronic Bronchitis caused by *Haemophilus influenzae* (including β-lactamase-producing strains), *Haemophilus parainfluenzae* (including β-lactamase-producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), or *Moraxella catarrhalis* (including β-lactamase-producing strains).

Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes*.
NOTE: SPECTRACEF is effective in the eradication of *Streptococcus pyogenes* from the oropharynx. SPECTRACEF has not been studied for the prevention of rheumatic fever following *Streptococcus pyogenes* pharyngitis/tonsillitis. Only intramuscular penicillin has been demonstrated to be effective for the prevention of rheumatic fever.

Uncomplicated Skin and Skin-Structure Infections caused by *Staphylococcus aureus* (including β-lactamase-producing strains) or *Streptococcus pyogenes*.

CONTRAINDICATIONS

SPECTRACEF is contraindicated in patients with known allergy to the cephalosporin class of antibiotics or any of its components.

SPECTRACEF is contraindicated in patients with carnitine deficiency or inborn errors of metabolism that may result in clinically significant carnitine deficiency, because use of SPECTRACEF causes renal excretion of carnitine. (See **PRECAUTIONS, General.**)

SPECTRACEF tablets contain sodium caseinate, a milk protein. Patients with milk protein hypersensitivity (not lactose intolerance) should not be administered SPECTRACEF.

WARNINGS

BEFORE THERAPY WITH SPECTRACEF (CEFDITOREN PIVOXIL) IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFDITOREN PIVOXIL, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF CEFDITOREN PIVOXIL IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFDITOREN PIVOXIL OCCURS, THE DRUG SHOULD BE DISCONTINUED. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefditoren pivoxil, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile (C. difficile)* is a primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General

SPECTRACEF is not recommended when prolonged antibiotic treatment is necessary, since other pivalate-containing compounds have caused clinical manifestations of carnitine deficiency when used over a period of months. No clinical effects of carnitine decrease have been associated with short-term treatment. The effects on carnitine concentrations of repeat short-term courses of SPECTRACEF are not known.

In healthy volunteers (mean age 32.5 ± 7.6 years) given a 200 mg BID regimen for 10 days, the mean decrease in plasma concentrations of total carnitine was 18.1 ± 7.2 nmole/mL, representing a 39% decrease in plasma carnitine concentrations. In healthy volunteers (mean age 34.7 ± 7.2 years) given a 400 mg BID regimen for 14 days, the mean decrease in plasma concentrations of carnitine was 33.3 ± 9.7 nmole/mL, representing a 63% decrease in plasma carnitine concentrations. Plasma concentrations of carnitine returned to the normal control range within 7 to 10 days after discontinuation of cefditoren pivoxil. (See **CLINICAL PHARMACOLOGY.**) Neither measurement of serum carnitine nor concomitant administration of supplemental carnitine is recommended as a general measure for patients receiving short-term treatment with cefditoren pivoxil.

As with other antibiotics, prolonged treatment may result in the possible emergence and overgrowth of resistant organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate alternative therapy should be administered.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated. In clinical trials, there was no difference between cefditoren and comparator cephalosporins in the incidence of increased prothrombin time.

Information for Patients

SPECTRACEF should be taken with meals to enhance absorption.

SPECTRACEF may be taken concomitantly with oral contraceptives.

It is not recommended that SPECTRACEF be taken concomitantly with antacids or other drugs taken to reduce stomach acids. (See **PRECAUTIONS, Drug Interactions.**)

SPECTRACEF tablets contain sodium caseinate, a milk protein. Patients with milk protein hypersensitivity (not lactose intolerance) should not be administered SPECTRACEF.

Drug Interactions

Oral Contraceptives

Multiple doses of cefditoren pivoxil had no effect on the pharmacokinetics of ethinyl estradiol, the estrogenic component in most oral contraceptives.

Antacids

Co-administration of a single dose of an antacid which contained both magnesium (800 mg) and aluminum (900 mg) hydroxides reduced the oral absorption of a single 400 mg dose of cefditoren pivoxil administered following a meal, as evidenced by a 14% decrease in mean C_{max} and an 11% decrease in mean AUC. Although the clinical significance is not known, it is not recommended that cefditoren pivoxil be taken concomitantly with antacids.

H_2-Receptor Antagonists

Co-administration of a single dose of intravenously administered famotidine (20 mg) reduced the oral absorption of a single 400 mg dose of cefditoren pivoxil administered following a meal, as evidenced by a 27% decrease in mean C_{max} and a 22% decrease in mean AUC. Although the clinical significance is not known, it is not recommended that cefditoren pivoxil be taken concomitantly with H_2 receptor antagonists.

(No. 7535) 750-01233-R1; Rev. August, 2001

SPECTRACEF™ Tablets

(cefditoren pivoxil) RX ONLY

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SPECTRACEF™ Tablets
(cefditoren pivoxil) RX ONLY

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Probenecid

As with other β-lactam antibiotics, co-administration of probenecid with cefditoren pivoxil resulted in an increase in the plasma exposure of cefditoren, with a 49% increase in mean C_{max}, a 122% increase in mean AUC, and a 53% increase in $t_{1/2}$.

Drug/Laboratory Test Interactions

Cephalosporins are known to occasionally induce a positive direct Coombs' test. A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with CLINITEST® tablets), but not with enzyme-based tests for glycosuria (e.g., CLINISTIX®, TES-TAPE®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood/plasma glucose levels in patients receiving cefditoren pivoxil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal carcinogenicity studies have been conducted with cefditoren pivoxil. Cefditoren pivoxil was not mutagenic in the Ames bacterial reverse mutation assay, or in the mouse lymphoma mutation assay at the hypoxanthine-guanine phosphoribosyltransferase locus. In Chinese hamster lung cells, chromosomal aberrations were produced by cefditoren pivoxil, but not by cefditoren. Subsequent studies showed that the chromosome aberrations were due to the release of formaldehyde from the pivoxil ester moiety in the *in vitro* assay system. Neither cefditoren nor cefditoren pivoxil produced chromosomal aberrations when tested in an *in vitro* human peripheral blood lymphocyte assay, or in the *in vivo* mouse micronucleus assay. Cefditoren pivoxil did not induce unscheduled DNA synthesis when tested.

In rats, fertility and reproduction were not affected by cefditoren pivoxil at oral doses up to 1000 mg/kg/day, approximately 24 times a human dose of 200 mg BID based on mg/m²/day.

Pregnancy - Teratogenic Effects

Pregnancy Category B

Cefditoren pivoxil was not teratogenic up to the highest doses tested in rats and rabbits. In rats, this dose was 1000 mg/kg/day, which is approximately 24 times a human dose of 200 mg BID based on mg/m²/day. In rabbits, the highest dose tested was 90 mg/kg/day, which is approximately four times a human dose of 200 mg BID based on mg/m²/day. This dose produced severe maternal toxicity and resulted in fetal toxicity and abortions.

In a postnatal development study in rats, cefditoren pivoxil produced no adverse effects on postnatal survival, physical and behavioral development, learning abilities, and reproductive capability at sexual maturity when tested at doses of up to 750 mg/kg/day, the highest dose tested. This is approximately 18 times a human dose of 200 mg BID based on mg/m²/day.

There are however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Cefditoren pivoxil has not been studied for use during labor and delivery.

Nursing Mothers

Cefditoren was detected in the breast milk of lactating rats. Because many drugs are excreted in human breast milk, caution should be exercised when cefditoren pivoxil is administered to nursing women.

Pediatric Use

Safety and efficacy of cefditoren pivoxil tablets in pediatric patients less than 12 years of age have not been established.

Geriatric Use

Of the 2409 patients in clinical studies who received cefditoren pivoxil 200 mg BID, 244 (10%) were >65 years of age. Of the 1890 patients in clinical studies who received cefditoren pivoxil 400 mg BID, 242 (13%) were >65 years of age. No clinically significant differences in effectiveness or safety were observed between older and younger patients. No dose adjustments are necessary in geriatric patients with normal (for their age) renal function. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **DOSAGE AND ADMINISTRATION**.)

ADVERSE EVENTS

Clinical Trials – SPECTRACEF Tablets (Adults and Adolescent Patients ≥12 Years of Age)

In clinical trials, 4299 adult and adolescent patients have been treated with the recommended doses of cefditoren pivoxil tablets (200 mg or 400 mg BID). Most adverse events were mild and self-limiting. No deaths or permanent disabilities have been attributed to cefditoren.

The following adverse events were thought by the investigators to be possibly, probably, or definitely related to cefditoren tablets in multiple-dose clinical trials:

Treatment-Related Adverse Events in Trials in Adult and Adolescent Patients ≥12 Years

		SPECTRACEF 200 mg BID (N=2409)	SPECTRACEF 400 mg BID (N=1890)	COMPARATORS[a] (N=2381)
Incidence ≥1%	Diarrhea	11%	14%	7%
	Nausea	4%	6%	5%
	Headache	2%	2%	2%
	Abdominal Pain	2%	2%	1%
	Vaginal Moniliasis	3%[b]	6%[c]	5%[d]
	Dyspepsia	1%	2%	2%
	Vomiting	1%	1%	1%

[a] includes amoxicillin/clavulanate, cefadroxil monohydrate, cefuroxime axetil, cefpodoxime proxetil, clarithromycin, and penicillin

[b] 1296 females

[c] 1010 females

[d] 1320 females

The overall incidence of adverse events, and in particular diarrhea, increased with the higher recommended dose of SPECTRACEF.

Treatment related adverse events experienced by <1% but >0.1% of patients who received 200 mg or 400 mg BID of cefditoren pivoxil were abnormal dreams, allergic reaction, anorexia, asthenia, coagulation time increased, constipation, dizziness, dry mouth, eructation, fever, flatulence, fungal infection, gastritis, gastrointestinal disorder, hyperglycemia, increased appetite, insomnia, leukopenia, leukorrhea, liver function test abnormal, mouth ulceration, myalgia, nervousness, oral moniliasis, pain, peripheral edema, pharyngitis, pseudomembranous colitis, pruritus, rash, rhinitis, sinusitis, somnolence, stomatitis, sweating, taste perversion, thrombocythemia, urinary frequency, urticaria, vaginitis, and weight loss. Pseudomembranous colitis symptoms may begin during or after antibiotic treatment. (See **WARNINGS**.)

Fifty-three of 2409 (2%) patients who received 200 mg BID and 64 of 1890 (3%) patients who received 400 mg BID of cefditoren pivoxil discontinued medication due to adverse events thought by the investigators to be possibly, probably, or definitely associated with cefditoren therapy. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or nausea. Diarrhea was the primary reason for discontinuation in 18 of 2409 (0.7%) patients who received 200 mg BID and in 26 of 1890 (1.4%) patients who received 400 mg BID of cefditoren pivoxil.

Changes in laboratory parameters of possible clinical significance, without regard to drug relationship and which occurred in ≥1% of patients who received cefditoren pivoxil 200 mg or 400 mg BID, were hematuria (2.0% and 3.2%), increased urine white blood cells (2.3% and 2.5%), decreased hematocrit (1.7% and 2.2%), and increased glucose (1.6% and 0.8%). Those events which occurred in <1% but >0.1% of patients included the following: increased/decreased white blood cells, increased eosinophils, decreased neutrophils, increased lymphocytes, increased platelet count, decreased hemoglobin, increased potassium, decreased chloride, decreased inorganic phosphorus, decreased calcium, increased SGPT, increased SGOT, increased cholesterol, decreased albumin, proteinuria, and increased BUN. It is not known if these abnormalities were caused by the drug or the underlying condition being treated.

Cephalosporin Class Adverse Reactions

In addition to the adverse reactions listed above which have been observed in patients treated with cefditoren pivoxil the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:

Adverse Reactions: Allergic reactions, anaphylaxis, drug fever, Stevens-Johnson syndrome, serum sickness-like reaction, erythema multiforme, toxic epidermal necrolysis, colitis, renal dysfunction, toxic nephropathy, reversible hyperactivity, hypertonia, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and superinfection.

Altered Laboratory Tests: Prolonged prothrombin time, positive direct Coombs' test, false-positive test for urinary glucose, elevated alkaline phosphatase, elevated bilirubin, elevated LDH, increased creatinine, pancytopenia, neutropenia, and agranulocytosis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. (See **DOSAGE AND ADMINISTRATION**.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

Information on cefditoren pivoxil overdosage in humans is not available. However, with other β-lactam antibiotics, adverse effects following overdosage have included nausea, vomiting, epigastric distress, diarrhea, and convulsions. Hemodialysis may aid in the removal of cefditoren from the body, particularly if renal function is compromised (30% reduction of plasma concentrations following 4 hours of hemodialysis). Treat overdosage symptomatically and institute supportive measures as required.

In acute animal toxicity studies, cefditoren pivoxil when tested at the limit oral doses of 5100 mg/kg in rats and up to 2000 mg/kg in dogs did not exhibit any health effects of concern. Certain effects, such as diarrhea and soft stool lasting for a few days were observed in some animals as expected with most oral antibiotics due to inhibition of intestinal microflora.

DOSAGE AND ADMINISTRATION

(See **INDICATIONS AND USAGE** for Indicated Pathogens.)

SPECTRACEF Dosage and Administration* Adults and Adolescents (≥12 Years)

Type of Infection	Dosage	Duration (days)
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg BID	10
Pharyngitis/Tonsillitis	200 mg BID	
Uncomplicated Skin and Skin Structure Infections		

*Should be taken with meals

Patients with Renal Insufficiency

No dose adjustment is necessary for patients with mild renal impairment (Cl_{cr}: 50-80 mL/min/1.73 m²). It is recommended that not more than 200 mg BID be administered to patients with moderate renal impairment (Cl_{cr}: 30-49 mL/min/1.73 m²) and 200 mg QD be administered to patients with severe renal impairment (Cl_{cr}: <30 mL/min/1.73 m²). The appropriate dose in patients with end-stage renal disease has not been determined.

Patients with Hepatic Disease

No dose adjustments are necessary for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). The pharmacokinetics of cefditoren have not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

HOW SUPPLIED

SPECTRACEF tablets containing cefditoren pivoxil equivalent to 200 mg of cefditoren are available as white, elliptical, film-coated tablets imprinted with TAP 200 mg in blue. These tablets are available in multi-dose tamper-evident containers as follows:

NDC 0300-7535-20 Bottles of 20
NDC 0300-7535-60 Bottles of 60

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Protect from light and moisture. Dispense in a tight, light resistant container.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Fifth Edition*; Approved Standard, NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January, 2000.

U.S. Patent Nos. 4,839,350; 4,918,068; and 5,956,915
Other patents pending.

Manufactured for
TAP Pharmaceuticals Inc.
Lake Forest, Illinois, 60045

™-Trademark

®-Registered Trademark

(No. 7535)
750-01233-R1; Revised: August, 2001

NDC 0300-7535-60
60 Tablets

SPECTRACEF®
cefditoren pivoxil
200-mg tablets

℞ only

TAP

Exp/Lot

Tamper-evident. Do not accept if seal on bottle is broken before first use.

Each white, elliptical, film-coated tablet contains 200 mg of cefditoren pivoxil and is imprinted with TAP 200 mg in blue.

Keep this and all medications out of the reach of children.

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.] Protect from light and moisture. Dispense in a light, light-resistant container.

See accompanying prescribing information.

Manufactured for
TAP Pharmaceuticals Inc.
Lake Forest, IL 60045 TL-1005-R1

NDC 0300-7535-20
20 Tablets

SPECTRACEF®
cefditoren pivoxil
200-mg tablets

℞ only

TAP

Exp/Lot

Tamper-evident. Do not accept if seal on bottle is broken before first use.

Each white, elliptical, film-coated tablet contains 200 mg of cefditoren pivoxil and is imprinted with TAP 200 mg in blue.

Keep this and all medications out of the reach of children.

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.] Protect from light and moisture. Dispense in a light, light-resistant container.

See accompanying prescribing information.

Complimentary professional sample.

Not for sale.

Manufactured for
TAP Pharmaceuticals Inc.
Lake Forest, IL 60045

TL-1006-R1